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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07K 5/12, 7/56, A61K 37/02

A1

(11) International Publication Number: **WO 94/22910**

(43) International Publication Date: 13 October 1994 (13.10.94)

(21) International Application Number: PCT/US94/03223

(22) International Filing Date: 28 March 1994 (28.03.94)

(30) Priority Data:
08/038,448 29 March 1993 (29.03.93) US

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(81) Designated States: AU, BB, BG, BR, BY, CA, CN, CZ, FI, GE, HU, JP, KG, KP, KR, KZ, LK, LV, MD, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CYCLIC COMPOUNDS USEFUL AS INHIBITORS OF PLATELET GLYCOPROTEIN IIb/IIIa

(57) Abstract

This invention relates to novel cyclic compounds containing carbocyclic ring systems useful as antagonists of the platelet glycoprotein IIb/IIIa complex, to pharmaceutical compositions containing such cyclic compounds, with or without other therapeutic agents, and to methods of using these compounds, with or without other therapeutic agents, for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of other thromboembolic disorders. This invention also relates to methods of using the cyclic compounds of the invention in combination with anti-coagulants such as warfarin or heparin, or additional anti-platelet agents such as aspirin, piroxicam or ticlopidine, or thrombin inhibitors such as boropeptides, hirudin or argatroban, or thrombolytic agents such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof, for the treatment of thromboembolic disorders.

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TITLE

Cyclic Compounds Useful as Inhibitors of Platelet Glycoprotein IIb/IIIa

FIELD OF THE INVENTION

This invention relates to novel cyclic compounds containing carbocyclic ring systems useful as antagonists of the platelet glycoprotein IIb/IIIa complex, to pharmaceutical compositions containing such cyclic compounds, with or without other therapeutic agents, and to methods of using these compounds, with or without other therapeutic agents, for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of other thromboembolic disorders.

BACKGROUND OF THE INVENTION

Activation of platelets and the resulting platelet aggregation and secretion of factors by the platelets has been associated with different pathophysiological conditions including cardiovascular and cerebrovascular thromboembolic disorders, for example, the thromboembolic disorders associated with unstable angina, myocardial infarction, transient ischemic attack, stroke, atherosclerosis and diabetes. The contribution of platelets to these disease processes stems from their ability to form aggregates, or platelet thrombi, especially in the arterial wall following injury or plaque rupture.

Platelets are known to play an essential role in the maintenance of hemostasis and in the pathogenesis of arterial thrombosis. Platelet activation has been shown to be enhanced during coronary thrombolysis which can

lead to delayed reperfusion and reocclusion. Clinical studies with aspirin, ticlopidine and a monoclonal antibody for platelet glycoprotein IIb/IIIa provide biochemical evidence for platelet involvement in unstable angina, early stage of acute myocardial infarction, transient ischemic attack, cerebral ischemia, and stroke.

Platelets are activated by a wide variety of agonists resulting in platelet shape change, secretion of granular contents and aggregation. Aggregation of platelets serves to further focus clot formation by concentrating activated clotting factors in one site. Several endogenous agonists including adenosine diphosphate (ADP), serotonin, arachidonic acid, thrombin, and collagen, have been identified. Because of the involvement of several endogenous agonists in activating platelet function and aggregation, an inhibitor which acts against all agonists would represent a more efficacious antiplatelet agent than currently available antiplatelet drugs, which are agonist-specific.

Current antiplatelet drugs are effective against only one type of agonist; these include aspirin, which acts against arachidonic acid; ticlopidine, which acts against ADP; thromboxane A_2 synthetase inhibitors or receptor antagonists, which act against thromboxane A_2; and hirudin, which acts against thrombin.

Recently, a common pathway for all known agonists has been identified, namely platelet glycoprotein IIb/IIIa complex (GPIIb/IIIa), which is the membrane protein mediating platelet aggregation. A recent review of GPIIb/IIIa is provided by Phillips et al. (1991) Cell 65: 359-362. The development of a GPIIb/IIIa antagonist represents a promising new approach for antiplatelet therapy. Recent studies in man with a monoclonal

antibody for GPIIb/IIIa indicate the antithrombotic benefit of a GPIIb/IIIa antagonist.

There is presently a need for a GPIIb/IIIa-specific antiplatelet agent which inhibits the activation and aggregation of platelets in response to any agonist. Such an agent should represent a more efficacious antiplatelet therapy than the currently available agonist-specific platelet inhibitors.

GPIIb/IIIa does not bind soluble proteins on unstimulated platelets, but GPIIb/IIIa in activated platelets is known to bind four soluble adhesive proteins, namely fibrinogen, von Willebrand factor, fibronectin, and vitronectin. The binding of fibrinogen and von Willebrand factor to GPIIb/IIIa causes platelets to aggregate. The binding of fibrinogen is mediated in part by the Arg-Gly-Asp (RGD) recognition sequence which is common to the adhesive proteins that bind GPIIb/IIIa.

Several RGD-containing peptides and related compounds have been reported which block fibrinogen binding and prevent the formation of platelet thrombi. For example, see Cadroy et al. (1989) J. Clin. Invest. 84: 939-944; Klein et al. U.S. Patent 4,952,562, issued 8/28/90; European Patent Application EP 0319506 A; European Patent Application EP 0422938 A1; European Patent Application EP 0422937 A1; European Patent Application EP 0341915 A2; PCT Patent Application WO 89/07609; PCT Patent Application WO 90/02751; PCT Patent Application WO 91/04247; and European Patent Application EP 0343085 A1.

In the present invention we use conformationally-constraining carbocyclic ring systems as templates for cyclizing peptides such that they have high affinity and selectivity for GPIIb/IIIa.

SUMMARY OF THE INVENTION

This invention provides novel cyclic compounds containing carbocyclic ring systems useful as antagonists of the platelet glycoprotein IIb/IIIa complex, pharmaceutical compositions containing such cyclic compounds, and methods of using these compounds, alone or in combination with other therapeutic agents, for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

This invention also relates to combination products, that is, pharmaceutical compositions containing the novel cyclic compounds of the invention in combination with anti-coagulants such as warfarin or heparin, or anti-platelet agents such as aspirin, piroxicam or ticlopidine, or thrombin inhibitors such as boropeptides, hirudin or argatroban, or thrombolytic agents such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof, to pharmaceutical kits containing these combination products, and to methods of using these combination products for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders.

BRIEF DESCRIPTION OF THE FIGURES

Figure I. Figure I shows the platelet deaggregatory and thrombolytic effects of the cyclic IIb/IIIa antagonist compounds cyclo-(D-AbuNMeArg-Gly-Asp-Mamb) (Compound A) and cyclo-(D-Val-NMeArgGly-Asp-Mamb) (Compound B) at varying concentrations on an already formed platelet-rich clot. The clot was formed by incubating the platelets with agonists for 30 minutes. The cyclic compounds of the present invention had a significant lytic effect on the clot, with an IC_{50} of about 0.0005 mM for Compound A. By comparison, the

linear peptide RGDS was much less effective as a thrombolytic, even at substantially higher concentrations.

Figure II. Figure II shows the thrombolytic effect of the cyclic IIb/IIIa antagonist compounds cyclo-(D-AbuNMeArg-Gly-Asp-Mamb) (Compound A) and cyclo-(D-Val-NMeArgGly-Asp-Mamb) (Compound B), and the standard thrombolytics tissue plasminogen activator (tPA), urokinase (UK) and streptokinase (SK) on an already formed platelet-rich clot. The clot was formed by incubating the platelets with agonists for 30 minutes. Both Compounds A and B showed a significant thrombolytic effect as compared to the standard thrombolytics tissue plasminogen activator, urokinase, and streptokinase.

Figure III. Figure III shows the thrombolytic effect of the cyclic compound cyclo-(D-AbuNMeArg-Gly-Asp-Mamb) (Compound A) and the standard thrombolytics tissue plasminogen activator (tPA), urokinase (UK), and streptokinase (SK), both alone and in combination, on an already formed platelet-rich clot. The clot was formed by incubating the platelets with agonists for 30 minutes. Compound A showed a significant thrombolytic effect, providing significant clot lysis at 1.0 uM. Moreover, Compound A in combination with tissue plasminogen activator, urokinase, or streptokinase was significantly better than Compound A alone, and significantly better than the additive effects of both agents administered alone.

Figure IV. Figure IV shows the thrombolytic effect of the cyclic IIb/IIIa antagonist compound cyclo-(D-Val-NMeArg-Gly-Asp-Mamb) (Compound B) and the standard thrombolytics tissue plasminogen activator (tPA), urokinase (UK) and streptokinase (SK), both alone and in

combination, on an already formed platelet-rich clot. The clot was formed by incubating the platelets with agonists for 30 minutes. Compound B showed a significant thrombolytic effect, providing significantly better clot lysis than tissue plasminogen activator, urokinase or streptokinase. Moreover, Compound B in combination with tissue plasminogen activator, urokinase or streptokinase was significantly better than Compound B alone, and significantly better than the additive effects of both agents.

Figure V. Figure V shows the thrombolytic effect of the cyclic compound cyclo-(DVal-NMeArg-Gly-Asp-MeMamb) (isomer 1; the compound of Example 68) (Compound C) alone and in combination with the standard thrombolytics tissue plasminogen activator (tPA), urokinase (UK) and streptokinase (SK) on an already formed platelet-rich clot. The clot was formed by incubating the platelets with agonists for 30 minutes. Compound C alone showed a significant thrombolytic effect. In combination with tissue plasminogen activator, urokinase or streptokinase, a thrombolytic effect was achieved which was greater than the additive effect of the agents when administered alone.

Figure VI. Figure VI shows the thrombolytic effect of the cyclic compound cyclo-(D-Val-NMeArg-Gly-Asp-MeMamb) (isomer 2; the compound of Example 68a) (Compound D) alone and in combination with the standard thrombolytics tissue plasminogen activator (tPA), urokinase (UK) and streptokinase (SK) on an already formed plateletrich clot. The clot was formed by incubating the platelets with agonists for 30 minutes. Compound D alone showed a significant thrombolytic effect. In combination with tissue plasminogen activator, urokinase or streptokinase, a thrombolytic

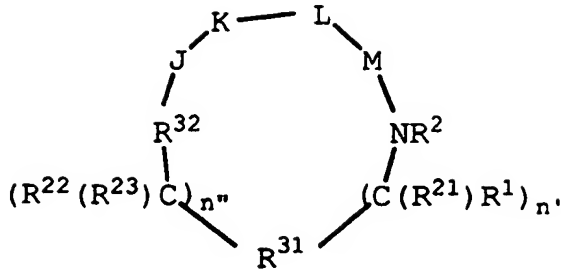
effect was achieved which was greater than the additive effect of the agents when administered alone.

Figure VII. Figure VII shows the in vivo thrombolytic and anti-thrombotic effect of the cyclic glycoprotein IIb/IIIa compound cyclo-(D-Abu-NMeArg-Gly-AspMamb) (Compound A), alone or in combination with the standard thrombolytic streptokinase (SK). The experiments were carried out using an arterial thrombosis animal model. Figure VII shows the results of initial administration as a percentage of clot lysis. Compound A alone showed good *in vivo* thrombolytic efficacy, and the use of Compound A with streptokinase resulted in an increase in *in vivo* thrombolytic efficacy while allowing a significantly lower dose of streptokinase. This study demonstrated significant reduction in the dose of streptokinase required to achieve 100% lysis *in vivo* when Compound A is administered along with streptokinase.

Figure VIII. Figure VIII a-d shows the results of administration of Compound A or saline following streptokinase (SK) or tissue plasminogen activator (t-PA) thrombolysis, with the results reported as time to reocclusion and percentage of reocclusion. The saline control showed 100% reocclusion, whereas administration of Compound A resulted in virtually no reocclusion.

DETAILED DESCRIPTION OF THE INVENTION

[1] This invention is directed to novel compounds of the formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug form thereof wherein:

R^{31} is a C_6-C_{14} saturated, partially saturated, or aromatic carbocyclic ring system substituted with 0-4 R^{10} or R^{10a};

R^{32} is selected from:

-C(=O)-;
-C(=S)-
$-S(=O)_2-$;
-S(=O)-;
$-P(=Z)(ZR^{13})-$;

Z is S or O;

n" and n' are independently 0-2;

R^1 and R^{22} are independently selected from the following groups:

hydrogen,
C_1-C_8 alkyl substituted with 0-2 R^{11};
C_2-C_8 alkenyl substituted with 0-2 R^{11};
C_2-C_8 alkynyl substituted with 0-2 R^{11};
C_3-C_{10} cycloalkyl substituted with 0-2 R^{11};

aryl substituted with 0-2 R^{12};

a 5-10-membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, said heterocyclic ring being substituted with 0-2 R^{12};

=O, F, Cl, Br, I, $-CF_3$, $-CN$, $-CO_2R^{13}$, $-C(=O)R^{13}$, $-C(=O)N(R^{13})_2$, $-CHO$, $-CH_2OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{14}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{14}SO_2N(R^{13})_2$, $-NR^{14}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-SR^{13}$, $-S(=O)R^{13a}$, $-SO_2N(R^{13})_2$, $-N(R^{13})_2$, $-NHC(=NH)NHR^{13}$, $-C(=NH)NHR^{13}$, $=NOR^{13}$, NO_2, $-C(=O)NHOR^{13}$, $-C(=O)NHNR^{13}R^{13a}$, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy;

R^1 and R^{21} can alternatively join to form a 3-7 membered carbocyclic ring substituted with 0-2 R^{12};

when n' is 2, R^1 or R^{21} can alternatively be taken together with R^1 or R^{21} on an adjacent carbon atom to form a direct bond, thereby to form a double or triple bond between said carbon atoms;

R^{22} and R^{23} can alternatively join to form a 3-7 membered carbocyclic ring substituted with 0-2 R^{12};

when n" is 2, R^{22} or R^{23} can alternatively be taken together with R^{22} or R^{23} on an adjacent carbon atom to form a direct bond, thereby to form a double or triple bond between the adjacent carbon atoms;

R^1 and R^2, where R^{21} is H, can alternatively join to form a 5-8 membered carbocyclic ring substituted with 0-2 R^{12};

R^{11} is selected from one or more of the following:

=O, F, Cl, Br, I, $-CF_3$, $-CN$, $-CO_2R^{13}$, $-C(=O)R^{13}$, $-C(=O)N(R^{13})_2$, $-CHO$, $-CH_2OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{14}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{14}SO_2N(R^{13})_2$, $-NR^{14}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-SR^{13}$, $-S(=O)R^{13a}$, $-SO_2N(R^{13})_2$, $-N(R^{13})_2$, $-NHC(=NH)NHR^{13}$, $-C(=NH)NHR^{13}$, $=NOR^{13}$, NO_2, $-C(=O)NHOR^{13}$, $-C(=O)NHNR^{13}R^{13a}$, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy,

C_1-C_5 alkyl, C_2-C_4 alkenyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_2-C_6 alkoxyalkyl, C_3-C_6 cycloalkoxy, C_1-C_4 alkyl (alkyl being substituted with 1-5 groups selected independently from: $-NR^{13}R^{14}$, $-CF_3$, NO_2, $-SO_2R^{13a}$, or $-S(=O)R^{13a}$),

aryl substituted with 0-2 R^{12},

a 5-10-membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, said heterocyclic ring being substituted with 0-2 R^{12};

R^{12} is selected from one or more of the following:

phenyl, benzyl, phenethyl, phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_7-C_{10} arylalkyl, C_1-C_5 alkoxy, $-CO_2R^{13}$, $-C(=O)NHOR^{13a}$, $-C(=O)NHN(R^{13})_2$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, C_3-C_6

cycloalkoxy, $-OC(=O)R^{13}$, $-C(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-(C_1-C_4$ alkyl$)-OR^{13}$, $-N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{13}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}SO_2N(R^{13})_2$, $-NR^{13}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-S(=O)R^{13a}$, $-SR^{13}$, $-SO_2N(R^{13})_2$, C_2-C_6 alkoxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, C_1-C_4 alkyl (alkyl being substituted with $-N(R^{13})_2$, $-CF_3$, NO_2, or $-S(=O)R^{13a}$);

R^{13} is selected independently from: H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, $-(C_1-C_{10}$ alkyl$)$aryl, or C_3-C_{10} alkoxyalkyl;

R^{13a} is C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, $-(C_1-C_{10}$ alkyl$)$aryl, or C_3-C_{10} alkoxyalkyl;

when two R^{13} groups are bonded to a single N, said R^{13} groups may alternatively be taken together to form $-(CH_2)_{2-5}-$ or $-(CH_2)O(CH_2)-$;

R^{14} is OH, H, C_1-C_4 alkyl, or benzyl;

R^{21} and R^{23} are independently selected from:

hydrogen;
C_1-C_4 alkyl, optionally substituted with 1-6 halogen;
benzyl;

R^2 is H or C_1-C_8 alkyl;

R^{10} and R^{10a} are selected independently from one or more of the following:

phenyl, benzyl, phenethyl, phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_7-C_{10} arylalkyl, C_1-C_5 alkoxy, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, $-C(=O)NHOR^{13a}$, $-C(=O)NHN(R^{13})_2$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, C_3-C_6 cycloalkoxy, $-OC(=O)R^{13}$, $-C(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-(C_1$-C_4 alkyl)$-OR^{13}$, $-N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{13}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}SO_2N(R^{13})_2$, $-NR^{13}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-S(=O)R^{13a}$, $-SR^{13}$, $-SO_2N(R^{13})_2$, C_2-C_6 alkoxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl (including $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)), C_1-C_4 haloalkoxy, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, C_1-C_4 alkyl (alkyl being substituted with $-N(R^{13})_2$, $-CF_3$, NO_2, or $-S(=O)R^{13a}$);

J is β-Ala or an L-isomer or D-isomer amino acid of structure $-N(R^3)C(R^4)(R^5)C(=O)-$, wherein:

R^3 is H or C_1-C_8 alkyl;

R^4 is H or C_1-C_3 alkyl;

R^5 is selected from:

hydrogen;

C_1-C_8 alkyl substituted with 0-2 R^{11};

C_2-C_8 alkenyl substituted with 0-2 R^{11};

C_2-C_8 alkynyl substituted with 0-2 R^{11};

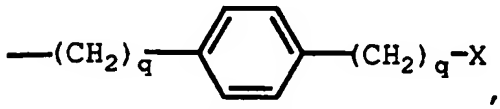
C_3-C_{10} cycloalkyl substituted with 0-2 R^{11};

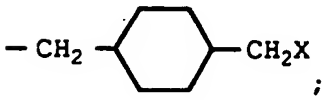
aryl substituted with 0-2 R^{12};

a 5-10-membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, or O, said heterocyclic ring being substituted with 0-2 R^{12};

=O, F, Cl, Br, I, $-CF_3$, $-CN$, $-CO_2R^{13}$, $-C(=O)R^{13}$, $-C(=O)N(R^{13})_2$, $-CHO$, $-CH_2OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{14}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{14}SO_2N(R^{13})_2$, $-NR^{14}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-SR^{13}$, $-S(=O)R^{13a}$, $-SO_2N(R^{13})_2$, $-N(R^{13})_2$, $-NHC(=NH)NHR^{13}$, $-C(=NH)NHR^{13}$, $=NOR^{13}$, NO_2, $-C(=O)NHOR^{13}$, $-C(=O)NHNR^{13}R^{13a}$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, $-SC(=NH)NHR^{13}$, N_3, $-Si(CH_3)_3$, (C_1-C_5 alkyl)NHR^{16};

$-(C_0$-C_6 alkyl)X;

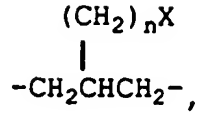

, where q is independently 0,1;


;

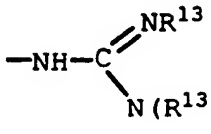
$-(CH_2)_mS(O)_{p'}(CH_2)_2X$, where m = 1,2 and p' = 0-2;

wherein X is defined below; and

R^3 and R^4 may also be taken together to form



, where



n = 0,1 and X is ;

R^3 and R^5 can alternatively be taken together to form $-(CH_2)_t-$ or $-CH_2S(O)_{p'}C(CH_3)_2-$, where t = 2-4 and p' = 0-2; or

R^4 and R^5 can alternatively be taken together to form $-(CH_2)_u-$, where u = 2-5;

R^{16} is selected from:

an amine protecting group;

1-2 amino acids;

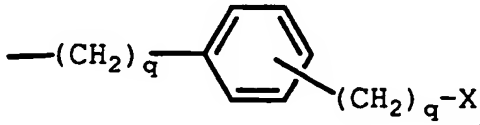
1-2 amino acids substituted with an amine protecting group;

K is a D-isomer or L-isomer amino acid of structure $-N(R^6)CH(R^7)C(=O)-$, wherein:

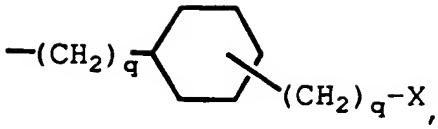
R^6 is H or C_1-C_8 alkyl;

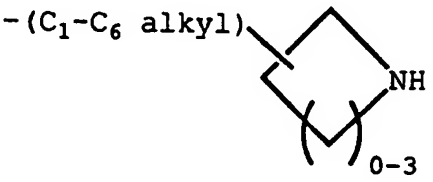
R^7 is selected from:

$-(C_1$-C_7 alkyl)X;



, wherein each q is independently 0-2 and substitution on the phenyl is at the 3 or 4 position;

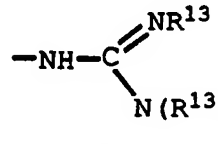

, wherein each q is independently 0-2 and substitution on the cyclohexyl is at the 3 or 4 position;



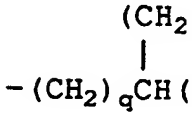
$-(CH_2)_mO-(C_1-C_4\ alkyl)-X$, where m = 1 or 2;

$-(CH_2)_mS(O)_{p'}-(C_1-C_4\ alkyl)-X$, where m = 1 or 2 and p' = 0-2; and

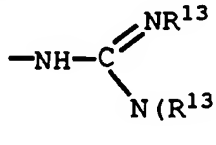
X is selected from:


; $-N(R^{13})R^{13}$; $-C(=NH)(NH_2)$; $-SC(=NH)-NH_2$; $-NH-C(=NH)(NHCN)$; $-NH-C(=NCN)(NH_2)$; $-NH-C(=N-OR^{13})(NH_2)$;

R^6 and R^7 can alternatively be taken together to form


, wherein each q is independently 1 or 2 and wherein

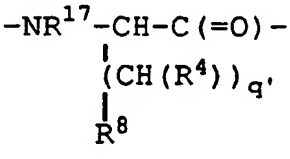
n = 0 or 1 and X is $-NH_2$ or


;

L is $-Y(CH_2)_vC(=O)-$, wherein:

Y is NH, $N(C_1-C_3$ alkyl), O, or S; and v = 1 or 2;

M is a D-isomer or L-isomer amino acid of structure



, wherein:

q' is 0-2;

R^{17} is H, C_1-C_3 alkyl;

R^8 is selected from:
$-CO_2R^{13}$, $-SO_3R^{13}$, $-SO_2NHR^{14}$, $-B(R^{34})(R^{35})$, $-NHSO_2CF_3$, $-CONHNHSO_2CF_3$, $-PO(OR^{13})_2$, $-PO(OR^{13})R^{13}$, $-SO_2NH$-heteroaryl (said heteroaryl being 5-10-membered and having 1-4 heteroatoms selected independently from N, S, or O) , $-SO_2NH$-heteroaryl (said heteroaryl being 5-10-membered and having 1-4 heteroatoms selected independently from N, S, or O), $-SO_2NHCOR^{13}$, $-CONHSO_2R^{13a}$, $-CH_2CONHSO_2R^{13a}$, $-NHSO_2NHCOR^{13a}$, $-NHCONHSO_2R^{13a}$, $-SO_2NHCONHR^{13}$, $-CO_2R^{13b}$;

R^{34} and R^{35} are independently selected from:
-OH,
-F,
$-N(R^{13})_2$, or
C_1-C_8-alkoxy;

R^{34} and R^{35} can alternatively be taken together form:

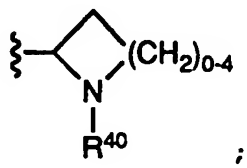
a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;

a divalent cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;

a cyclic boron amide-ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;

R^{13b} is selected from:

(a) C_1-C_8 alkyl;
(b) C_2-C_8 alkenyl;
(c) C_2-C_8 alkynyl;
(d) C_3-C_8 cycloalkyl;
(e) C_1-C_8 alkyl substituted with
  (i) aryl, optionally substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1-C_5$ alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);
  (ii) C_3-C_8 cycloalkyl;
  (iii)



;

(f) aryl, optionally substituted with 1-2 substituents independently selected from

halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1-C_5$ alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(g) C_2-C_8 alkyl, alkenyl or alkynyl; substituted with 1-2 substituents independently selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, phenoxy, benzyloxy, halogen, NO_2, CN, CO_2R^{13}, $CON(R^{13})_2$, $N(R^{36})COR^{36}$, morpholino, 2-(1-morpholino)ethoxy, $N(R^{13})_2$, $N^+(R^{13})_3$, OCOCH3, CF_3, $S(O)_{0-2}R^{13a}$;

(h) $CH(R^{36})OR^{38}$;

(i) $CH(R^{36})OC(=O)R^{37}$;

(j) $CH(R^{36})OC(=O)OR^{38}$;

(k) $CH(R^{36})OC(=O)N(R^{37})_2$;

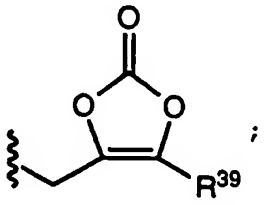
(l) $CH(R^{36})N(R^{36})C(=O)R^{36}$;

(m) $CH(R^{36})CO_2R^{37}$;

(n) $CH(R^{36})CON(R^{13})_2$;

(o) $CH(R^{36})N(R^{13})_2$;

(q)



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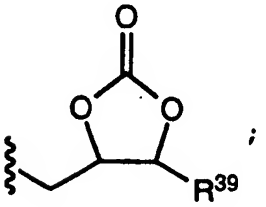

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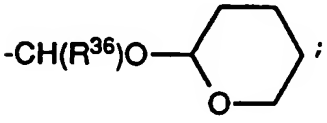

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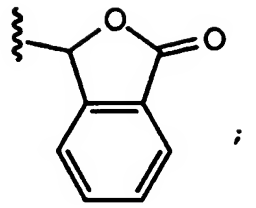

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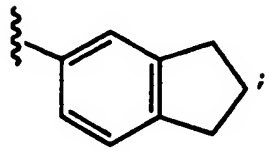


;

R^{36} is selected independently from: H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, phenyl, or benzyl;

R^{37} is selected from:

(a) H;

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, -S(C_1-C_5 alkyl), -SO(C_1-C_5 alkyl), -SO_2(C_1-C_5 alkyl), -OH, -N(R^{13})$_2$, -CO_2R^{13}, -C(=O)N(R^{13})$_2$, or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, -S(C_1-C_5 alkyl), -SO(C_1-C_5 alkyl), -SO_2(C_1-C_5 alkyl), -OH, -N(R^{13})$_2$, -CO_2R^{13}, -C(=O)N(R^{13})$_2$, or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

R^{38} is selected from:

(a) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
(i) C_1-C_4 alkyl;
(ii) C_3-C_8 cycloalkyl;
(iii) C_1-C_5 alkoxy;
(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(b) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{39} is selected from:

(a) H

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
(i) C_1-C_6 alkyl;
(ii) C_1-C_6 alkoxy;
(iii) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$,

$-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{40} is selected from: H, C_1-C_5 alkyl, or benzyl;

provided that at least one of the following conditions is met:

(1) R^{32} is not $-C(=O)-$; or

(2) p' is not 0; or

(3) q' is not 0; or

(4) q is not 0-1; or

(5) X is $-NH-C(=NH)NHCN$, $-NH-C(=NCN)(NH_2)$ or $-NH-C(=NOR^{13})NH_2$; or

(5) R^8 is $-B(R^{34})(R^{35})$ or $-CO_2R^{13b}$.

The present invention includes the use of the above described compounds (wherein the above conditions (1)-(5) are not required) in combination with one or more additional therapeutic agents for the inhibition of platelet aggregation, as thrombolytics, and/or for the treatment of thromboembolic disorders, wherein the additional therapeutic agent is selected from: anti-coagulants such as warfarin or heparin, or anti-platelet agents such as aspirin, piroxicam or ticlopidine; thrombin inhibitors such as boropeptides, hirudin or argatroban; or thrombolytic agents such as tissue plasminogen activator, anistreplase, urokinase or streptokinase.

[2] The present invention includes those compounds above wherein:

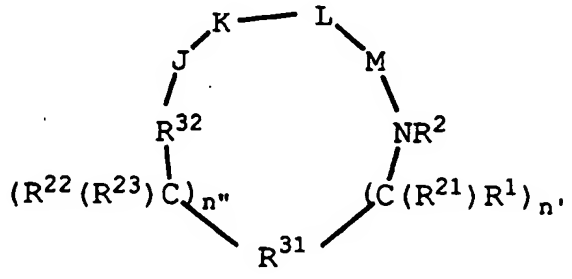
R^{31} is bonded to $(C(R^{23})R^{22})_{n''}$ and $(C(R^{21})R^{1})_{n'}$ at 2 different atoms on said carbocyclic ring.

[3] Included in the present invention are those compounds above, wherein:

n" is 0 and n' is 0;
n" is 0 and n' is 1;
n" is 0 and n' is 2;
n" is 1 and n' is 0;
n" is 1 and n' is 1;
n" is 1 and n' is 2;
n" is 2 and n' is 0;
n" is 2 and n' is 1; or
n" is 2 and n' is 2.

[4] Included in the present invention are those compounds of formula (I) above wherein R^6 is methyl, ethyl, or propyl.

[5] This invention includes those compounds above of the formula:



(I)

or a pharmaceutically acceptable salt or prodrug form thereof wherein:

R^{31} is a C_6-C_{14} saturated, partially saturated, or aromatic carbocyclic ring system substituted with 0-4 R^{10} or R^{10a};

R^{32} is selected from:

$-C(=O)-$;
$-C(=S)-$
$-S(=O)_2-$;

Z is S or O;

n" and n' are independently 0-2;

R^1 and R^{22} are independently selected from the following groups:

hydrogen,
C_1-C_8 alkyl substituted with 0-2 R^{11},
C_2-C_8 alkenyl substituted with 0-2 R^{11},
C_2-C_8 alkynyl substituted with 0-2 R^{11},
C_3-C_8 cycloalkyl substituted with 0-2 R^{11},
C_6-C_{10} bicycloalkyl substituted with 0-2 R^{11},

aryl substituted with 0-2 R^{12},

a 5-10-membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, or O, said heterocyclic ring being substituted with 0-2 R^{12};

=O, F, Cl, Br, I, $-CF_3$, $-CN$, $-CO_2R^{13}$, $-C(=O)R^{13}$, $-C(=O)N(R^{13})_2$, $-CHO$, $-CH_2OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{14}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{14}SO_2N(R^{13})_2$, $-NR^{14}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-SR^{13}$, $-S(=O)R^{13a}$, $-SO_2N(R^{13})_2$, $-CH_2N(R^{13})_2$, $-N(R^{13})_2$, $-NHC(=NH)NHR^{13}$, $-C(=NH)NHR^{13}$, NO_2;

R^1 and R^{21} can alternatively join to form a 5-7 membered carbocyclic ring substituted with 0-2 R^{12};

when n' is 2, R^1 or R^{21} can alternatively be taken together with R^1 or R^{21} on an adjacent carbon atom to form a direct bond, thereby to form a double or triple bond between said carbon atoms;

R^{22} and R^{23} can alternatively join to form a 3-7 membered carbocyclic ring substituted with 0-2 R^{12};

when n" is 2, R^{22} or R^{23} can alternatively be taken together with R^{22} or R^{23} on an adjacent carbon atom to form a direct bond, thereby to form a double or triple bond between said carbon atoms;

R^1 and R^2, where R^{21} is H, can alternatively join to form a 5-8 membered carbocyclic ring substituted with 0-2 R^{12};

R^{11} is selected from one or more of the following:

=O, F, Cl, Br, I, $-CF_3$, -CN, $-CO_2R^{13}$, $-C(=O)R^{13}$, $-C(=O)N(R^{13})_2$, -CHO, $-CH_2OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{14}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{14}SO_2N(R^{13})_2$, $-NR^{14}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-SR^{13}$, $-S(=O)R^{13a}$, $-SO_2N(R^{13})_2$, $-CH_2N(R^{13})_2$, $-N(R^{13})_2$, $-NHC(=NH)NHR^{13}$, $-C(=NH)NHR^{13}$, $=NOR^{13}$, NO_2;

C_1-C_5 alkyl, C_2-C_4 alkenyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_2-C_6 alkoxyalkyl, C_1-C_4 alkyl (substituted with $-NR^{13}R^{14}$, $-CF_3$, NO_2, $-SO_2R^{13}$, or $-S(=O)R^{13a}$)

aryl substituted with 0-2 R^{12},

a 5-10-membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, or O, said heterocyclic ring being substituted with 0-2 R^{12};

R^{12} is selected from one or more of the following:

phenyl, benzyl, phenethyl, phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_7-C_{10} arylalkyl, C_1-C_5 alkoxy, $-CO_2R^{13}$, $-C(=O)NHOR^{13a}$, $-C(=O)NHN(R^{13})_2$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, C_3-C_6 cycloalkoxy, $-OC(=O)R^{13}$, $-C(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-(C_1$-C_4 alkyl)$-OR^{13}$, $-N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{13}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}SO_2N(R^{13})_2$, $-NR^{13}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-S(=O)R^{13a}$, $-SR^{13}$, $-SO_2N(R^{13})_2$, C_2-C_6 alkoxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, C_1-C_4 alkyl (alkyl being substituted with $-N(R^{13})_2$, $-CF_3$, NO_2, or $-S(=O)R^{13a}$);

R^{13} is selected independently from: H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, $-(C_1$-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

R^{13a} is C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, $-(C_1$-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

when two R^{13} groups are bonded to a single N, said R^{13} groups may alternatively be taken together to form $-(CH_2)_{2-5}-$ or $-(CH_2)O(CH_2)-$;

R^{14} is OH, H, C_1-C_4 alkyl, or benzyl;

R^{21} and R^{23} are independently selected from:

hydrogen;
C_1-C_4 alkyl, optionally substituted with 1-6 halogen;
benzyl;

R^2 is H or C_1-C_8 alkyl;

R^{10} and R^{10a} are selected independently from one or more of the following:

phenyl, benzyl, phenethyl, phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_7-C_{10} arylalkyl, C_1-C_5 alkoxy, $-CO_2R^{13}$, $-C(=O)NHOR^{13a}$, $-C(=O)NHN(R^{13})_2$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, C_3-C_6 cycloalkoxy, $-OC(=O)R^{13}$, $-C(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-(C_1$-C_4 alkyl$)-OR^{13}$, $-N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{13}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}SO_2N(R^{13})_2$, $-NR^{13}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-S(=O)R^{13a}$, $-SR^{13}$, $-SO_2N(R^{13})_2$, C_2-C_6 alkoxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, C_1-C_4 alkyl (alkyl being substituted with $-N(R^{13})_2$, $-CF_3$, NO_2, or $-S(=O)R^{13a}$);

J is β-Ala or an L-isomer or D-isomer amino acid of structure $-N(R^3)C(R^4)(R^5)C(=O)-$, wherein:

R^3 is H or CH_3;

R^4 is H or C_1-C_3 alkyl;

R^5 is H, C_1-C_8 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_1-C_6 cycloalkylethyl, phenyl, phenylmethyl, CH_2OH, CH_2SH, CH_2OCH_3, CH_2SCH_3, $CH_2CH_2SCH_3$, $(CH_2)_sNH_2$, $(CH_2)_sNHC(=NH)(NH_2)$, $(CH_2)_sNHR^{16}$, where s = 3-5;

R^3 and R^5 can alternatively be taken together to form $-(CH_2)_t-$ (t = 2-4) or $-CH_2SC(CH_3)_2-$; or

R^4 and R^5 can alternatively be taken together to form $-(CH_2)_u-$, where u = 2-5;

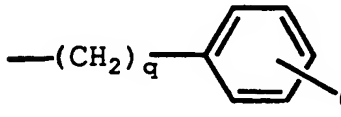
R^{16} is selected from:
an amine protecting group;
1-2 amino acids;
1-2 amino acids subtituted with an amine protecting group;

K is a D-isomer or L-isomer amino acid of structure $-N(R^6)CH(R^7)C(=O)-$, wherein:

R^6 is H or C_1-C_8 alkyl;

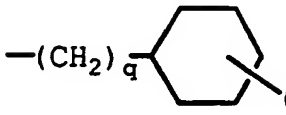
R^7 is selected from:

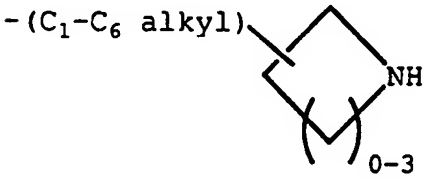
$-(C_1$-C_7 alkyl$)X$;



, wherein each q is

independently 0-2 and substitution on the phenyl is at the 3 or 4 position;


, wherein each q is independently 0-2 and substitution on the cyclohexyl is at the 3 or 4 position;



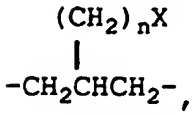
$-(CH_2)_mO-(C_1-C_4$ alkyl)-X, where m = 1 or 2;

$-(CH_2)_mS-(C_1-C_4$ alkyl)-X, where m = 1 or 2; and

X is selected from:

$-NH-C(=NH)(NH_2)$, $-NHR^{13}$, $-C(=NH)(NH_2)$, $-SC(NH)-NH_2$;

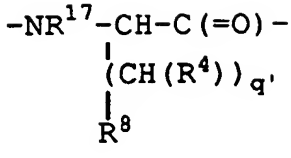
R^6 and R^7 can alternatively be taken together to form


, where n = 0 or 1 and X is $-NH_2$ or $-NH-C(=NH)(NH_2)$;

L is $-Y(CH_2)_vC(=O)-$, wherein:

Y is NH, $N(C_1-C_3$ alkyl), O, or S; and v = 1 or 2;

M is a D-isomer or L-isomer amino acid of structure



, wherein:

q' is 0-2;

R^{17} is H, C_1-C_3 alkyl;

R^8 is selected from:
$-CO_2R^{13}$, $-SO_3R^{13}$, $-SO_2NHR^{14}$, $-B(R^{34})(R^{35})$, $-NHSO_2CF_3$, $-CONHNHSO_2CF_3$, $-PO(OR^{13})_2$, $-PO(OR^{13})R^{13}$, $-SO_2NH$-heteroaryl (said heteroaryl being 5-10-membered and having 1-4 heteroatoms selected independently from N, S, or O) , $-SO_2NH$-heteroaryl (said heteroaryl being 5-10-membered and having 1-4 heteroatoms selected independently from N, S, or O), $-SO_2NHCOR^{13}$, $-CONHSO_2R^{13a}$, $-CH_2CONHSO_2R^{13a}$, $-NHSO_2NHCOR^{13a}$, $-NHCONHSO_2R^{13a}$, $-SO_2NHCONHR^{13}$, $-CO_2R^{13b}$;

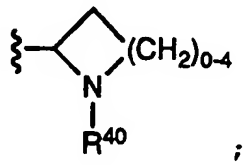
R^{34} and R^{35} are independently selected from:
-OH,
-F,
$-NR^{13}R^{14}$, or
C_1-C_8-alkoxy;

R^{34} and R^{35} can alternatively be taken together form:
a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;
a divalent cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;

a cyclic boron amide-ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;

R^{13b} is selected from:

(a) C_1-C_8 alkyl;
(b) C_2-C_8 alkenyl;
(c) C_2-C_8 alkynyl;
(d) C_3-C_8 cycloalkyl;
(e) C_1-C_8 alkyl substituted with
(i) aryl, optionally substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1$-C_5 alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);
(ii) C_3-C_8 cycloalkyl;
(iii)



;

(f) aryl, optionally substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1$-C_5 alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);
(g) C_2-C_8 alkyl, alkenyl or alkynyl; substituted with 1-2 substituents independently selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, phenoxy, benzyloxy, halogen,

NO_2, CN, CO_2R^{13}, $CON(R^{13})_2$, $N(R^{36})COR^{36}$, morpholino, 2-(1-morpholino)ethoxy, $N(R^{13})_2$, $N^+(R^{13})_3$, $OCOCH_3$, CF_3, $S(O)_{0-2}R^{13a}$;

(h) $CH(R^{36})OR^{38}$;

(i) $CH(R^{36})OC(=O)R^{37}$;

(j) $CH(R^{36})OC(=O)OR^{38}$;

(k) $CH(R^{36})OC(=O)N(R^{37})_2$;

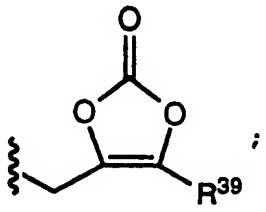
(l) $CH(R^{36})N(R^{36})C(=O)R^{36}$;

(m) $CH(R^{36})CO_2R^{37}$;

(n) $CH(R^{36})CON(R^{13})_2$;

(o) $CH(R^{36})N(R^{13})_2$;

(q)



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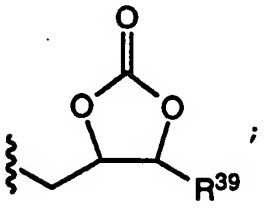

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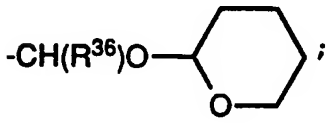

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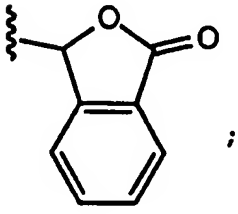

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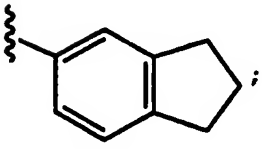


;

R^{36} is selected independently from: H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, phenyl, or benzyl;

R^{37} is selected from:

(a) H;

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{38} is selected from:

(a) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl),

-OH, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(b) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), -OH, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{39} is selected from:

(a) H

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_6 alkyl;

(ii) C_1-C_6 alkoxy;

(iii) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), -OH, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), -OH, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{40} is selected from: H, C_1-C_5 alkyl, or benzyl.

[6] Included in the present invention are compounds above, wherein:

R^{31} is selected from the group consisting of:

(a) a 6 membered saturated, partially saturated or aromatic carbocyclic ring substituted with 0-3 R^{10} or R^{10a};

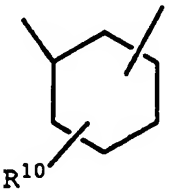
(b) a 8-11 membered saturated, partially saturated, or aromatic fused bicyclic carbocyclic ring substituted with 0-4 R^{10} or R^{10a}; or

(c) a 14 membered saturated, partially saturated, or aromatic fused tricyclic carbocyclic ring substituted with 0-4 R^{10} or R^{10a}.

[7] The present invention includes compounds of formula (I) above wherein:

R^{31} is selected from the group consisting of:

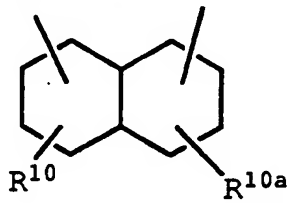
(a) a 6 membered saturated, partially saturated, or aromatic carbocyclic ring of formula:



wherein any of the bonds forming the carbocyclic ring may be a single or double bond,

and wherein said carbocyclic ring is substituted independently with 0-4 R^{10};

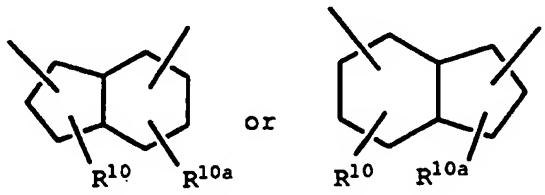
(b) a 10 membered saturated, partially saturated, or aromatic bicyclic carbocyclic ring of formula:



, wherein any of the bonds forming the carbocyclic ring may be a single or double bond,

and wherein said carbocyclic ring is substituted independently with 0-4 R^{10} or R^{10a};

(c) a 9 membered saturated, partially saturated, or aromatic bicyclic carbocyclic ring of formula:

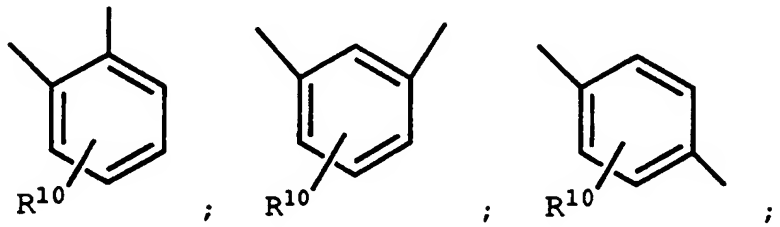


wherein any of the bonds forming the carbocyclic ring may be a single or double bond,

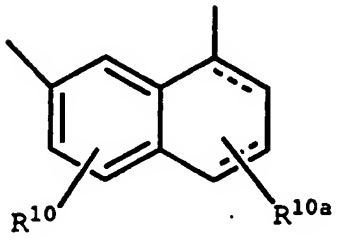
and wherein said carbocyclic ring is substituted independently with 0-4 R^{10} or R^{10a}.

[8] This invention includes compounds of formula (I) wherein:

R^{31} is selected from (the dashed bond may be a single or double bond):



or



wherein R^{31} may be substituted independently with 0-3 R^{10} or R^{10a};

n" is 0 or 1;
n' is 0-2.

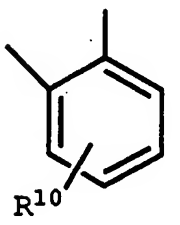
[9] The present invention includes compounds of formula (I) above wherein:

R^1 and R^{22} are independently selected from:
phenyl, benzyl, phenethyl, phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_7-C_{10} arylalkyl, C_1-C_5 alkoxy, $-CO_2R^{13}$, $-C(=O)NHOR^{13a}$,

$-C(=O)NHN(R^{13})_2$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, C_3-C_6 cycloalkoxy, $-OC(=O)R^{13}$, $-C(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-(C_1$-C_4 alkyl$)$-OR^{13}, $-N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{13}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}SO_2N(R^{13})_2$, $-NR^{13}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-S(=O)R^{13a}$, $-SR^{13}$, $-SO_2N(R^{13})_2$, C_2-C_6 alkoxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, C_1-C_4 alkyl (alkyl being substituted with $-N(R^{13})_2$, $-CF_3$, NO_2, or $-S(=O)R^{13a}$).

The present invention includes compounds of formula (I), or a pharmaceutically acceptable salt or prodrug form thereof wherein:

R^{31} is selected from:



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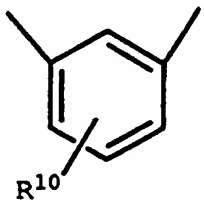

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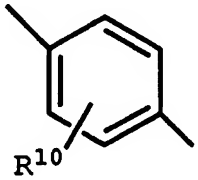

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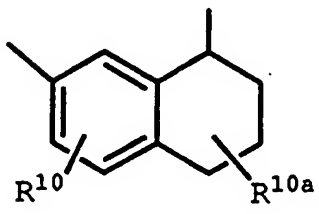
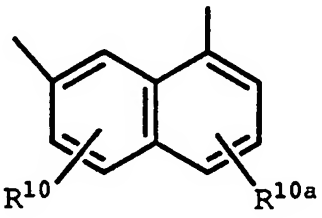


; or


wherein R^{31} may be substituted independently with 0-3 R^{10} or R^{10a};

n" is 0 or 1;
n' is 0-2;

R^1 and R^{22} are independently selected from H, C_1-C_4 alkyl, phenyl, benzyl, phenyl-(C_2-C_4)alkyl, C_1-C_4 alkoxy;

R^{21} and R^{23} are independently H or C_1-C_4 alkyl;

R^2 is H or C_1-C_8 alkyl;

R^{13} is selected independently from: H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, -(C_1-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

R^{13a} is C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, -(C_1-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

when two R^{13} groups are bonded to a single N, said R^{13} groups may alternatively be taken together to form $-(CH_2)_{2-5}-$ or $-(CH_2)O(CH_2)-$;

R^{14} is OH, H, C_1-C_4 alkyl, or benzyl;

R^{10} and R^{10a} are selected independently from: H, C_1-C_8 alkyl, phenyl, halogen, or C_1-C_4 alkoxy;

J is β-Ala or an L-isomer or D-isomer amino acid of structure $-N(R^3)C(R^4)(R^5)C(=O)-$, wherein:

R^3 is H or CH_3;
R^4 is H or C_1-C_3 alkyl;

R^5 is H, C_1-C_8 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_1-C_6 cycloalkylethyl, phenyl, phenylmethyl, CH_2OH, CH_2SH, CH_2OCH_3, CH_2SCH_3, $CH_2CH_2SCH_3$, $(CH_2)_sNH_2$, $-(CH_2)_sNHC(=NH)(NH_2)$, $-(CH_2)_sNHR^{16}$, where s = 3-5; or

R^{16} is selected from:
an amine protecting group;
1-2 amino acids; or
1-2 amino acids substituted with an amine protecting group;

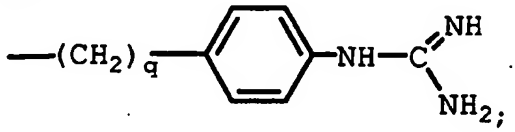
R^3 and R^5 can alternatively be taken together to form $-(CH_2)_t-$ (t = 2-4) or $-CH_2SC(CH_3)_2-$; or

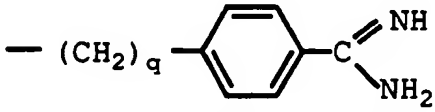
R^4 and R^5 can alternatively be taken together to form $-(CH_2)_u-$, where u = 2-5;

K is an L-isomer amino acid of structure $-N(R^6)CH(R^7)C(=O)-$, wherein:

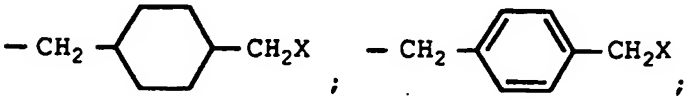
R^6 is H or C_1-C_8 alkyl;

R^7 is



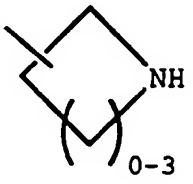

, where q = 0 or 1;

$-(CH_2)_rX$, where r = 3-6;



$-(CH_2)_mS(CH_2)_2X$, where m = 1 or 2;

$-(C_3-C_7$ alkyl$)-NH-(C_1-C_6$ alkyl$)$

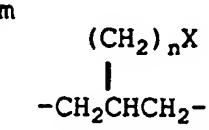
$-(C_1-C_4$ alkyl$)$ 

$-(CH_2)_m-O-(C_1-C_4$ alkyl$)-NH-(C_1-C_6$ alkyl$)$, where m = 1 or 2;

$-(CH_2)_m-S-(C_1-C_4$ alkyl$)-NH-(C_1-C_6$ alkyl$)$, where m = 1 or 2; and

X is $-NH_2$ or $-NHC(=NH)(NH_2)$; or

R^6 and R^7 can alternatively be taken together to form

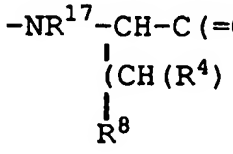


$-CH_2CHCH_2-$, where n = 0 or 1 and X is $-NH_2$ or $-NHC(=NH)(NH_2)$;

L is $-Y(CH_2)_vC(=O)-$, wherein:

Y is NH, O, or S; and v = 1 or 2;

M is a D-isomer or L-isomer amino acid of structure



, wherein:

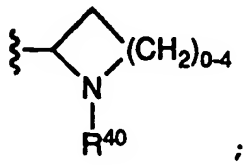
q' is 0-2;

R^{17} is H, C_1-C_3 alkyl;

R^8 is selected from:
$-CO_2R^{13}$, $-SO_3R^{13}$, $-SO_2NHR^{14}$, $-B(R^{34})(R^{35})$, $-NHSO_2CF_3$, $-CONHNHSO_2CF_3$, $-PO(OR^{13})_2$, $-PO(OR^{13})R^{13}$, $-SO_2NH$-heteroaryl (said heteroaryl being 5-10-membered and having 1-4 heteroatoms selected independently from N, S, or O) , $-SO_2NH$-heteroaryl (said heteroaryl being 5-10-membered and having 1-4 heteroatoms selected independently from N, S, or O), $-SO_2NHCOR^{13}$, $-CONHSO_2R^{13a}$, $-CH_2CONHSO_2R^{13a}$, $-NHSO_2NHCOR^{13a}$, $-NHCONHSO_2R^{13a}$, $-SO_2NHCONHR^{13}$, $-CO_2R^{13b}$;

R^{13b} is selected from:

(a) C_1-C_8 alkyl;
(b) C_2-C_8 alkenyl;
(c) C_2-C_8 alkynyl;
(d) C_3-C_8 cycloalkyl;
(e) C_1-C_8 alkyl substituted with
  (i) aryl, optionally substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1$-C_5 alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);
  (ii) C_3-C_8 cycloalkyl;
  (iii)



;

(f) aryl, optionally substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1-C_5$ alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(g) C_2-C_8 alkyl, alkenyl or alkynyl; substituted with 1-2 substituents independently selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, phenoxy, benzyloxy, halogen, NO_2, CN, CO_2R^{13}, $CON(R^{13})_2$, $N(R^{36})COR^{36}$, morpholino, 2-(1-morpholino)ethoxy, $N(R^{13})_2$, $N^+(R^{13})_3$, OCOCH3, CF_3, $S(O)_{0-2}R^{13a}$;

(h) $CH(R^{36})OR^{38}$;

(i) $CH(R^{36})OC(=O)R^{37}$;

(j) $CH(R^{36})OC(=O)OR^{38}$;

(k) $CH(R^{36})OC(=O)N(R^{37})_2$;

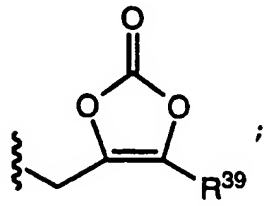
(l) $CH(R^{36})N(R^{36})C(=O)R^{36}$;

(m) $CH(R^{36})CO_2R^{37}$;

(n) $CH(R^{36})CON(R^{13})_2$;

(o) $CH(R^{36})N(R^{13})_2$;

(q)



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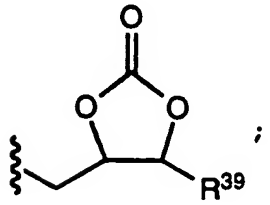
(r)



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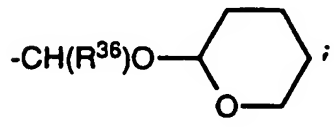
(s)



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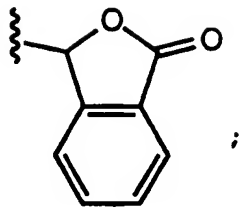
(t)



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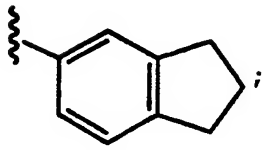
(u)



;

R^{36} is selected independently from: H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, phenyl, or benzyl;

R^{37} is selected from:

(a) H;

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{38} is selected from:

(a) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
(i) C_1-C_4 alkyl;
(ii) C_3-C_8 cycloalkyl;
(iii) C_1-C_5 alkoxy;
(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, -S(C_1-C_5 alkyl), -SO(C_1-C_5 alkyl), -SO_2(C_1-C_5 alkyl), -OH, -$N(R^{13})_2$, -CO_2R^{13}, -$C(=O)N(R^{13})_2$, or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

(b) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, -S(C_1-C_5 alkyl), -SO(C_1-C_5 alkyl), -SO_2(C_1-C_5 alkyl), -OH, -$N(R^{13})_2$, -CO_2R^{13}, -$C(=O)N(R^{13})_2$, or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

R^{39} is selected from:

(a) H

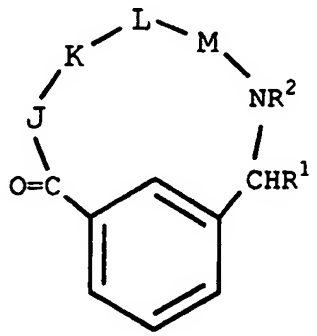
(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
(i) C_1-C_6 alkyl;
(ii) C_1-C_6 alkoxy;
(iii) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, -S(C_1-C_5 alkyl), -SO(C_1-C_5 alkyl), -SO_2(C_1-C_5 alkyl), -OH, -$N(R^{13})_2$, -CO_2R^{13}, -$C(=O)N(R^{13})_2$, or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, -S(C_1-C_5 alkyl), -SO(C_1-C_5 alkyl), -SO_2(C_1-C_5 alkyl), -OH, -$N(R^{13})_2$,

$-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{40} is selected from: H, C_1-C_5 alkyl, or benzyl.

[10] Preferred compounds of the invention are 1,3-disubstituted phenyl compounds of the formula (II):



(II)

wherein:

the phenyl ring in formula (II) may be further substituted with 0-3 R^{10};

R^{10} is selected independently from: H, C_1-C_8 alkyl, phenyl, halogen, or C_1-C_4 alkoxy;

R^1 is H, C_1-C_4 alkyl, phenyl, benzyl, or phenyl-(C_1-C_4)alkyl;

R^2 is H or methyl;

R^{13} is selected independently from: H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, -(C_1-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

R^{13a} is C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, -(C_1-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

when two R^{13} groups are bonded to a single N, said R^{13} groups may alternatively be taken together to form $-(CH_2)_{2-5}-$ or $-(CH_2)O(CH_2)-$;

R^{14} is OH, H, C_1-C_4 alkyl, or benzyl;

J is β-Ala or an L-isomer or D-isomer amino acid of structure $-N(R^3)C(R^4)(R^5)C(=O)-$, wherein:

R^3 is H or CH_3;

R^4 is H or C_1-C_3 alkyl;

R^5 is H, C_1-C_8 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_1-C_6 cycloalkylethyl, phenyl, phenylmethyl, CH_2OH, CH_2SH, CH_2OCH_3, CH_2SCH_3, $CH_2CH_2SCH_3$, $(CH_2)_sNH_2$, $-(CH_2)_sNHC(=NH)(NH_2)$, $-(CH_2)_sNHR^{16}$, where s = 3-5; or

R^{16} is selected from:
an amine protecting group;
1-2 amino acids; or
1-2 amino acids substituted with an amine protecting group;

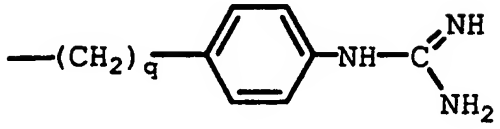
R^3 and R^5 can alternatively be taken together to form $-CH_2CH_2CH_2-$; or

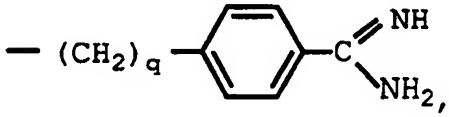
R^4 and R^5 can alternatively be taken together to form $-(CH_2)_u-$, where u = 2-5;

K is an L-isomer amino acid of structure $-N(R^6)CH(R^7)C(=O)-$, wherein:

R^6 is H or C_1-C_8 alkyl;

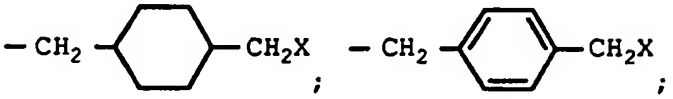
R^7 is:





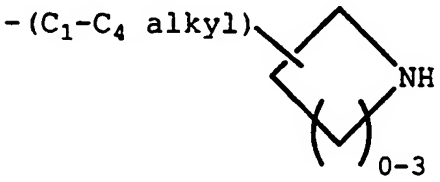
where q = 0 or 1;

$-(CH_2)_rX$, where r = 3-6;



$-(CH_2)_mS(CH_2)_2X$, where m = 1 or 2;

$-(C_3$-C_7 alkyl$)$-NH-$(C_1$-C_6 alkyl$)$



$-(C_1$-C_4 alkyl$)$-O-$(C_1$-C_4 alkyl$)$-NH-$(C_1$-C_6 alkyl), where m = 1 or 2;

$-(CH_2)_m$-S-$(C_1$-C_4 alkyl$)$-NH-$(C_1$-C_6 alkyl), where m = 1 or 2; and

X is $-NH_2$ or $-NHC(=NH)(NH_2)$, provided that X is not $-NH_2$ when r = 4; or

R^6 and R7 are alternatively be taken together to form

$-CH_2CH(CH_2)_nX-CH_2-$, where n = 0,1 and X is $-NH_2$ or $-NHC(=NH)(NH_2)$;

L is $-Y(CH_2)_vC(=O)-$, wherein:

Y is NH, O, or S; and v = 1,2;

M is a D-isomer or L-isomer amino acid of structure

$-NR^{17}-CH(R^8)-C(=O)-(CH(R^4))_{q'}-$, wherein:

q' is 0-2;

R^{17} is H, C_1-C_3 alkyl;

R^8 is selected from:
$-CO_2R^{13}$, $-SO_3R^{13}$, $-SO_2NHR^{14}$, $-B(R^{34})(R^{35})$, $-NHSO_2CF_3$, $-CONHNHSO_2CF_3$, $-PO(OR^{13})_2$, $-PO(OR^{13})R^{13}$, $-SO_2NH$-heteroaryl (said heteroaryl being 5-10-membered and having 1-4 heteroatoms selected independently from N, S, or O), $-SO_2NH$-heteroaryl (said heteroaryl being 5-10-membered and having 1-4 heteroatoms selected independently from N, S, or O), $-SO_2NHCOR^{13}$, $-CONHSO_2R^{13a}$, $-CH_2CONHSO_2R^{13a}$, $-NHSO_2NHCOR^{13a}$, $-NHCONHSO_2R^{13a}$, $-SO_2NHCONHR^{13}$, $-CO_2R^{13b}$;

R^{13b} is selected from:

(a) C_2-C_8 alkenyl;

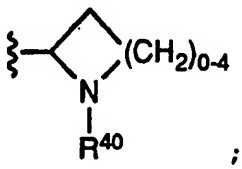
(b) C_2-C_8 alkynyl;

(c) C_1-C_8 alkyl substituted with

(i) aryl, optionally substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1$-C_5 alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(ii) C_3-C_8 cycloalkyl;

(iii)



;

(e) aryl, substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1$-C_5 alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(f) C_2-C_8 alkyl, alkenyl or alkynyl; substituted with 1-2 substituents independently selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, phenoxy, benzyloxy, halogen, NO_2, CN, CO_2R^{13}, $CON(R^{13})_2$, $N(R^{36})COR^{36}$, morpholino, 2-(1-morpholino)ethoxy, $N(R^{13})_2$, $N^+(R^{13})_3$, OCOCH3, CF_3, $S(O)_{0-2}R^{13a}$;

(g) $CH(R^{36})OR^{38}$;

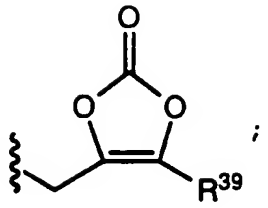
(h) $CH(R^{36})OC(=O)R^{37}$;

(i) $CH(R^{36})OC(=O)OR^{38}$;

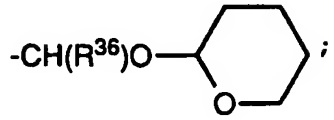
(j) $CH(R^{36})OC(=O)N(R^{37})_2$;

(k) $CH(R^{36})CO_2R^{37}$;

(l)



(m)



R^{36} is selected independently from: H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, phenyl, or benzyl;

R^{37} is selected from:

(a) H;

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{38} is selected from:

(a) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
(i) C_1-C_4 alkyl;
(ii) C_3-C_8 cycloalkyl;
(iii) C_1-C_5 alkoxy;
(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);
(b) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{39} is selected from:
(a) H
(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
(i) C_1-C_6 alkyl;
(ii) C_1-C_6 alkoxy;
(iii) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);
(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$,

$-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{40} is selected from: H, C_1-C_5 alkyl, or benzyl.

[11] Preferred compounds of the present invention are compounds of formula (II) above, wherein:

the phenyl ring in formula (II) may be further substituted with 0-2 R^{10} or R^{10a};

R^{10} or R^{10a} are selected independently from: H, C_1-C_8 alkyl, phenyl, halogen, or C_1-C_4 alkoxy;

R^1 is H;

R^2 is H;

R^{13} is selected independently from: H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, -(C_1-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

R^{13a} is C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, -(C_1-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

when two R^{13} groups are bonded to a single N, said R^{13} groups may alternatively be taken together to form $-(CH_2)_{2-5}-$ or $-(CH_2)O(CH_2)-$;

R^{14} is OH, H, C_1-C_4 alkyl, or benzyl;

J is β-Ala or an L-isomer or D-isomer amino acid of formula $-N(R^3)CH(R^5)C(=O)-$, wherein:

R^3 is H and R^5 is H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2SCH_3$, $CH_2CH(CH_3)_2$, $(CH_2)_4NH_2$, $(C_3\text{-}C_5$ alkyl$)NHR^{16}$; or

R^3 is CH_3 and R^5 is H; or

R^3 and R^5 can alternatively be taken together to form $-CH_2CH_2CH_2-$;

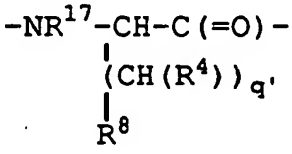
R^{16} is selected from:
an amine protecting group;
1-2 amino acids;
1-2 amino acids substituted with an amine protecting group;

K is an L-isomer amino acid of formula $-N(CH_3)CH(R^7)C(=O)-$, wherein:

R^7 is $-(CH_2)_3NHC(=NH)(NH_2)$;

L is $-NHCH_2C(=O)-$; and

M is a D-isomer or L-isomer amino acid of structure



, wherein:

q' is 1;

R^4 is H or CH_3;

R^{17} is H;

R^8 is

$-CO_2H$;

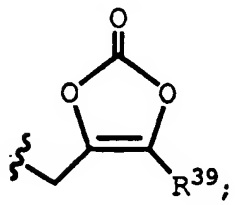
$-SO_3H$;

$-CO_2R^{13b}$;

R^{13b} is selected independently from:

$-CH(R^{36})OC(=O)R^{37}$;

$-CH(R^{36})OC(=O)OR^{38}$;



R^{36} is C_1-C_4 linear alkyl or H;

R^{37} is selected from:

(a) H;

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$,

$-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{38} is selected from:

(a) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
(i) C_1-C_4 alkyl;
(ii) C_3-C_8 cycloalkyl;
(iii) C_1-C_5 alkoxy;
(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(b) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{39} is C_1-C_4 alkyl, benzyl, or phenyl.

[12] Preferred compounds of the present invention are compounds of formula (II), or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently selected from H, methyl;

J is selected from D-Val, D-2-aminobutyric acid, D-Leu, D-Ala, Gly, D-Pro, D-Ser, D-Lys, β-Ala, Pro, Phe, NMeGly, D-Nle, D-Phg, D-Ile, D-Phe, D-Tyr, Ala, N^{ε}-p-azidobenzoyl-D-Lys, N^{ε}-p-benzoylbenzoyl-D-Lys,

N^{ε}-tryptophanyl-D-Lys, N^{ε}-o-benzylbenzoyl-D-Lys, N^{ε}-p-acetylbenzoyl-D-Lys, N^{ε}-dansyl-D-Lys, N^{ε}-glycyl-D-Lys, N^{ε}-glycyl-p-benzoylbenzoyl-D-Lys, N^{ε}-p-phenylbenzoyl-D-Lys, N^{ε}-m-benzoylbenzoyl-D-Lys, N^{ε}-o-benzoylbenzoyl-D-Lys;

K is selected from NMeArg, Arg;

L is selected from Gly, β-Ala, Ala;

M is selected from Asp; αMeAsp; βMeAsp; NMeAsp; D-Asp;
Asp-(methylcarbonyloxymethyl ester);
Asp-(ethylcarbonyloxymethyl ester);
Asp-(*t*-butylcarbonyloxymethyl ester);
Asp-(cyclohexylcarbonyloxymethyl ester);
Asp-(1-(methylcarbonyloxy)ethyl ester);
Asp-(1-(ethylcarbonyloxy)ethyl ester);
Asp-(1-(t-butylcarbonyloxy)ethyl ester);
Asp-(1-(cyclohexylcarbonyloxy)ethyl ester);
Asp-(*i*-propyloxycarbonyloxymethyl ester);
Asp-(cyclohexylcarbonyloxymethyl ester);
Asp-(*t*-butyloxycarbonyloxymethyl ester);
Asp-(1-(i-propyloxycarbonyloxy)ethyl ester);
Asp-(1-(cyclohexyloxycarbonyloxy)ethyl ester);
Asp-(1-(*t*-butyloxycarbonyloxy)ethyl ester);
Asp-(dimethylaminoethyl ester);
Asp-(diethylaminoethyl ester);
Asp-((1,3-dioxa-5-methyl-cyclopenten-2-one-4-yl)methyl ester);
Asp-((5-(*t*-butyl)-1,3-dioxa-cyclopenten-2-one-4-yl)methyl ester);
Asp-((1,3-dioxa-5-phenyl-cyclopenten-2-one-4-yl)methyl ester);
Asp-(1-(2-(2-methoxypropyl)carbonyloxy)ethyl ester).

[13] Preferred compounds of the present invention are compounds of formula (II), or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently selected from H, methyl;

J is selected from: D-Val, D-2-aminobutyric acid, D-Leu, D-Ala, Gly, D-Pro, D-Ser, D-Lys, β-Ala, Pro, Phe, NMeGly, D-Nle, D-Phg, D-Ile, D-Phe, D-Tyr, Ala;

K is selected from NMeArg;

L is Gly;

M is selected from Asp; αMeAsp; βMeAsp; NMeAsp; D-Asp;
Asp-(methylcarbonyloxymethyl ester);
Asp-(ethylcarbonyloxymethyl ester);
Asp-(*t*-butylcarbonyloxymethyl ester);
Asp-(cyclohexylcarbonyloxymethyl ester);
Asp-(1-(methylcarbonyloxy)ethyl ester);
Asp-(1-(ethylcarbonyloxy)ethyl ester);
Asp-(1-(t-butylcarbonyloxy)ethyl ester);
Asp-(1-(cyclohexylcarbonyloxy)ethyl ester);
Asp-(*i*-propyloxycarbonyloxymethyl ester);
Asp-(cyclohexylcarbonyloxymethyl ester);
Asp-(*t*-butyloxycarbonyloxymethyl ester);
Asp-(1-(i-propyloxycarbonyloxy)ethyl ester);
Asp-(1-(cyclohexyloxycarbonyloxy)ethyl ester);
Asp-(1-(*t*-butyloxycarbonyloxy)ethyl ester);
Asp-(dimethylaminoethyl ester);
Asp-(diethylaminoethyl ester);
Asp-((1,3-dioxa-5-methyl-cyclopenten-2-one-4-yl)methyl ester);

Asp-((5-(*t*-butyl)-1,3-dioxa-cyclopenten-2-one-4-yl)methyl ester);
Asp-((1,3-dioxa-5-phenyl-cyclopenten-2-one-4-yl)methyl ester);
Asp-(1-(2-(2-methoxypropyl)carbonyloxy)ethyl ester).

[14] Specifically preferred compounds of the present invention are the following compounds and pharmaceutically acceptable salts thereof:

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(methylcarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(ethylcarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(*t*-butylcarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(cyclohexylcarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(methylcarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(ethylcarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(t-butylcarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(cyclohexylcarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(*i*-propyloxycarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(cyclohexylcarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(*t*-butyloxycarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(i-propyloxycarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(cyclohexyloxycarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(*t*-butyloxycarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(dimethylaminoethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(diethylaminoethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-((1,3-dioxa-5-methyl-cyclopenten-2-one-4-yl)methyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-((5-(*t*-butyl)-1,3-dioxa-cyclopenten-2-one-4-yl)methyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-((1,3-dioxa-5-phenyl-cyclopenten-2-one-4-yl)methyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(2-(2-methoxypropyl)carbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(methylcarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(ethylcarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(*t*-butylcarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(cyclohexylcarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(methylcarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(ethylcarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(t-butylcarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(cyclohexylcarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(*i*-propyloxycarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(cyclohexylcarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(*t*-butyloxycarbonyloxymethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(i-propyloxycarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(cyclohexyloxycarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(*t*-butyloxycarbonyloxy)ethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(dimethylaminoethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(diethylaminoethyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-((1,3-dioxa-5-methyl-cyclopenten-2-one-4-yl)methyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-((5-(*t*-butyl)-1,3-dioxa-cyclopenten-2-one-4-yl)methyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-((1,3-dioxa-5-phenyl-cyclopenten-2-one-4-yl)methyl ester).

The compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(2-(2-methoxypropyl)carbonyloxy)ethyl ester).

In the present invention it has been discovered that the compounds above are useful as inhibitors of glycoprotein IIb/IIIa (GPIIb/IIIa). As discussed above, GPIIb/IIIa mediates the process of platelet activation and aggregation. The compounds of the present invention inhibit the activation and aggregation of platelets induced by all known endogenous platelet agonists.

The present invention also provides methods for the treatment (including prevention) of conditions involving platelet activation and aggregation, such as arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, thromboembolic disorders associated with unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, deep vein thrombosis, pulmonary embolism, or diabetes, by administering to a host in need of such treatment a pharmaceutically effective amount of the compounds described above. The compounds of the present invention are useful for inhibiting the binding of fibrinogen to blood platelets, inhibiting aggregation of blood platelets, treating thrombus formation or embolus formation, or preventing thrombus or embolus formation in a mammal. The compounds of the invention may be used as a medicament for blocking fibrinogen from acting at its receptor site in a mammal.

The compounds of the present invention can also be combined or co-administered with suitable anti-coagulant or coagulation inhibitory agents, such as heparin or warfarin, or anti-platelet or platelet inhibitory agents, such as aspirin, piroxicam or ticlopidine. Further, the compounds of this invention may be combined or co-administered with thrombin inhibitors such as boropeptides, hirudin or argatroban. The compounds of the present invention may also be combined or

co-administered with thrombolytic or fibrinolytic agents, such as plasminogen activators, anistreplase, urokinase, or streptokinase. The compounds of the present invention may also be combined or co-administered with combinations of the foregoing agents and/or with other therapeutic agents. Such combination products may be employed to achieve synergistic effects or effects additive to those provided by the compounds of the present invention, such as, for example, in such uses as described above, particularly in the treatment, including prevention, of thromboembolic disorders.

The GPIIb/IIIa antagonists of the present invention inhibit platelet aggregation at the final common pathway required for platelet aggregation induced by any of the known platelet activators or even their combinations. On the other hand, platelet granular secretions, of various important biomolecules from the α-granule (PAI-1) or the dense granule (serotonin) are not affected by the GPIIb/IIIa antagonist. These molecules secreted from platelets might play an important role in arterial vasospasm (serotonin) and in reducing the efficiency of the natural lytics (PAI-1). Hence, the combination of the compounds of the present invention with other drugs which may affect these mechanisms and may thereby provide a particularly effective therapy for many different heterogenous thromboembolic disorders.

The GPIIb/IIIa antagonists of the present invention with high affinity for the platelet GPIIb/IIIa receptor (Kd < 0.01 μM) are expected to be very effective not only in preventing thrombosis formation, but also in accelerating lysis of platelet rich thrombi, thereby providing a greater utility of such antiplatelet agents in the acute and chronic thromboembolic disorders. Such

a strategy may be an effective adjunct therapy with thrombolytic therapy. Indeed, platelet activation after thrombolytic therapy may have a significant role in the delay of reperfusion and abrupt closure (reocclusion).

The term anti-coagulant agents (or coagulation inhibitory agents), as used herein, denotes agents that inhibit blood coagulation. Such agents include warfarin, heparin, or low molecular weight heparin (LMWH), including pharmaceutically acceptable salts or prodrugs thereof. For reasons of efficacy, the preferable anti-coagulant agents are warfarin or heparin or LMWH. The warfarin employed herein, may be, for example, crystalline warfarin or amorphous sodium warfarin. The heparin employed herein may be, for example, the sodium or sulfate salts thereof.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), which has been well researched and widely used with good results, and piroxicam, which exerts its anti-platelet effect when dosed once daily, are preferred compounds, especially aspirin. Piroxicam is commercially available from Pfizer Inc. (New York, NY), as FELDANE™. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is

known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include thromboxane-A2-receptor antagonists and thromboxane-A2-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The phrase thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombinmediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. Such inhibitors include boropeptides, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Preferably the thrombin inhibitors are boropeptides. By boropeptides, it is meant, N-acetyl and peptide derivatives of boronic acid, such as C-terminal α-aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiouronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin.

Preferable boropeptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boropeptide thrombin inhibitors include those disclosed in PCT Patent Application Publication Number 92/07869 and European Patent Application Publication Number 471 651 A2, the disclosures of which are hereby incorporated herein by reference, in their entirety.

The phrase thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof.

Tissue plasminogen activator (tPA) is commercially available from Genentech Inc., South San Francisco, California. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 0 28 489, the disclosures of which are hereby incorporated herein by reference herein, in their entirety. Anistreplase is commercially available from the Beecham Group, Middlesex, England, under the trademark EMINASE™. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

Combination products, where the cyclic compounds of the invention are combined or co-administered with suitable anti-coagulant agents, antiplatelet agents, thrombin inhibitors, and/or thrombolytic agents, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side effects, thereby providing an increased margin of safety.

Clinical studies using anti-coagulant agents alone, including crystalline sodium warfarin, have provided evidence of their efficacy in the treatment or secondary prevention of coronary artery disease. Of three published, randomized, controlled trials of the treatment of acute myocardial infarction, oral anti-coagulants significantly reduced overall mortality and the frequency of reinfarction in one study. Of the four published large, randomized, controlled trials of oral anti-coagulants in the secondary prevention of myocardial infarction, three suggested a reduction in the incidence of reinfarction and early mortality. One additional study, the Warfarin Reinfarction Study, has also recently demonstrated a significant reduction in

mortality, reinfarction, and stroke in people with a previous myocardial infarction who were treated with warfarin as compared to those treated with placebo.

The results of studies utilizing anti-platelet agents such as acetylsalicylic acid (ASA) alone in the prevention and treatment of coronary artery disease have also been promising. In patients with unstable angina, ASA has been demonstrated to reduce the incidence of subsequent myocardial infarction and mortality in two large, randomized, double-blind, placebo-controlled clinical studies. In addition, ASA has been approved for use in the secondary prevention of myocardial infarction, based on data from several trials which, when pooled, suggested a reduction in reinfarction and mortality. Furthermore, two recent studies evaluating ASA in the primary prevention of coronary artery disease have reported either a dramatic or inconsequential benefit. In addition to their utility in coronary artery disease, agents that inhibit platelet function such as ASA and ticlopidine have been shown to be effective in the prevention of stroke in people with cerebrovascular disease. Pooled data from nine randomized trials have provided overwhelming evidence of the efficacy of ASA alone in reducing the risk of completed stroke in people with transient ischemic attacks (TIAs). Recently, ticlopidine alone has also been demonstrated to have efficacy in treating TIAs.

With regard to thrombin inhibitors, such as boropeptides, studies have demonstrated that such compounds provide excellent candidates for the control of thrombinmediated processes. Studies with hirudin, another thrombin inhibitor, have shown this agent to be an effective compound in the treatment of venous and arterial thrombosis.

Current therapy in the treatment of patients with acute myocardial infarction includes thrombolytics such

as plasminogen activators such as tPA, streptokinase, or urokinase. These standard thrombolytics, when employed alone, promote the generation of plasmin, which degrades platelet-rich fibrin clots.

Thromboembolic disorders are known, however, to have a diverse pathophysiological makeup. There is a need for a therapeutic approach to the treatment of these disorders which takes into account the diverse pathophysiological makeup of such diseases, and which includes components ameliorating each of the various pathophysiological aspects. A combination product containing an anti-coagulant agent such as warfarin or heparin, or an antiplatelet agent such as aspirin, piroxicam or ticlopidine, or a thrombin inhibitor such as a boropeptide, hirudin or argatroban, or a thrombolytic agent such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof, in combination with a novel cyclic compound of the invention, can provide such an approach. In addition, by administering lower doses of each, which is feasible where an additive or synergistic effect is involved, the incidence of any side effects associated with each alone at higher doses may be significantly reduced. Also, where a convenient single dosage form is offered, as in a preferred embodiment of the invention, it is generally accepted that such increased convenience to the patient results in an increase in compliance. Also, a single dosage form would reduce the likelihood of patient confusion often associated with concurrent dosing of medication not available in a single dosage form. The present combinations of an anticoagulant agent and a compound of this invention, or an anti-platelet agent and a compound of this invention, or a thrombin inhibitor and a compound of this invention, or a thrombolytic agent and a compound of this

invention, or combinations thereof, are directed to meeting these, as well as other, needs.

GPIIb/IIIa is known to be overexpressed in metastatic tumor cells. The compounds or combination products of the present invention may also be useful for the treatment, including prevention, of metastatic cancer.

The compounds herein described may have asymmetric centers. Unless otherwise indicated, all chiral, diastereomeric and racemic forms are included in the present invention. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. It will be appreciated that compounds of the present invention contain asymmetrically substituted carbon atoms, and may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. Two distinct isomers (cis and trans) of the peptide bond are known to occur; both can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Unless otherwise specifically noted, the L-isomer of the amino acid is used at positions J, K, L, and M of the compounds of the present invention. Except as provided in the preceding sentence, all chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomer form is specifically indicated. The D and L-isomers of a particular amino acid are designated herein using the conventional 3-letter abbreviation of the amino acid, as indicated by the following examples: D-Leu, D-Leu, L-Leu, or L-Leu.

When any variable (for example, R^1 through R^8, m, n, p, X, Y, etc.) occurs more than one time in any constituent or in any formula, its definition on each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^{11}, then said group may optionally be substituted with up to two R^{11} and R^{11} at each occurrence is selected independently from the defined list of possible R^{11}. Also, by way of example, for the group $-N(R^{13})_2$, each of the two R^{13} substituents on N is independently selected from the defined list of possible R^{13}.

When a bond to a substituent is shown to cross the bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring.

Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

By "stable compound" or "stable structure" is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "substituted", as used herein, means that an one or more hydrogen on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substitent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon

groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)); "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge; "cycloalkyl" is intended to include saturated ring groups, including mono-,bi- or poly-cyclic ring systems, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and adamantyl; and "biycloalkyl" is intended to include saturated bicyclic ring groups such as [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, and so forth. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl and the like; and "alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl, propynyl and the like.

The phrase "boronic acid" as used herein means a group of the formula $-B(R^{34})(R^{35})$, wherein R^{34} and R^{35} are independently selected from: -OH; -F; $-NR^{13}R^{14}$; or C_1-C_8-alkoxy; or R^{34} and R^{35} can alternatively be taken together to form: a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O; a divalent cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O; a cyclic boron amide-ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from

N, S, or O. Such cyclic boron esters, boron amides, or boron amide-esters may also be optionally substituted with 1-5 groups independently selected from R^{11}.

Boron esters include boronic acid protecting groups, including moieties derived from diols, for example pinanediol and pinacol to form pinanediol boronic acid ester and the pinacol boronic acid, respectively. Other illustrations of diols useful for deriving boronic acid esters are perfluoropinacol, ethylene glycol, diethylene glycol, 1,2-ethanediol, 1,3-propanediol, 1,2-propanediol, 1,2-butanediol, 1,4-butanediol, 2,3-butanediol, 2,3-hexanediol, 1,2-hexanediol, catechol, 1,2-diisopropylethanediol, 5,6-decanediol, 1,2-dicyclohexylethanediol.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate and the like.

As used herein, "aryl" or "aromatic residue" is intended to mean phenyl or naphthyl. As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7- membered monocyclic or bicyclic or 7- to 14-membered bicyclic or tricyclic or an up to 26-membered polycyclic carbon ring, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocyles include, but are not limited to, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, biphenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic ring system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 10-membered bicyclic heterocyclic ring which may be saturated, partially unsaturated, or aromatic, and which

consists of carbon atoms and from 1 to 4 heteroatoms selected independently from the group consisting of N, O and S and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples of such heterocycles include, but are not limited to, benzopyranyl, thiadiazine, tetrazolyl, benzofuranyl, benzothiophenyl, indolene, quinoline, isoquinolinyl or benzimidazolyl, piperidinyl, 4-piperidone, 2-pyrrolidone, tetrahydrofuran, tetrahydroquinoline, tetrahydroisoquinoline, decahydroquinoline, octahydroisoquinoline, azocine, triazine (including 1,2,3-, 1,2,4-, and 1,3,5-triazine), 6*H*-1,2,5-thiadiazine, 2*H*,6*H*-1,5,2-dithiazine, thiophene, tetrahydrothiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, 2*H*-pyrrole, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole (including 1,2,4- and 1,3,4-oxazole), isoxazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, 3*H*-indole, indole, 1*H*-indazole, purine, 4*H*-quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, 4a*H*-carbazole, carbazole, ß-carboline, phenanthridine, acridine, perimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, isochroman, chroman, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperazine, indoline, isoindoline, quinuclidine, or

morpholine. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

As used herein, the term "any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino or sulfhydryl" means any group bonded to an O, N, or S atom, respectively, which is cleaved from the O, N, or S atom when the compound is administered to a mammalian subject to provide a compound having a remaining free hydroxyl, amino, or sulfhydryl group, respectively. Examples of groups that, when administered to a mammalian subject, are cleaved to form a free hydroxyl, amino or sulfhydryl, include but are not limited to, C_1-C_6 alkyl substituted with 0-3 R^{11}, C_3-C_6 alkoxyalkyl substituted with 0-3 R^{11}, C_1-C_6 alkylcarbonyl substituted with 0-3 R^{11}, C_1-C_6 alkoxycarbonyl substituted with 0-3 R^{11}, C_1-C_6 alkylaminocarbonyl substituted with 0-3 R^{11}, benzoyl substituted with 0-3 R^{12}, phenoxycarbonyl substituted with 0-3 R^{12}, phenylaminocarbonyl substituted with 0-3 R^{12}. Examples of groups that, when administered to a mammalian subject, are cleaved to form a free hydroxyl, amino or sulfhydryl, include hydroxy, amine or sulfhydryl protecting groups, respectively.

As used herein, the term "amine protecting group" means any group known in the art of organic synthesis for the protection of amine groups. Such amine protecting groups include those listed in Greene, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Sythesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference. Any amine protecting group known in the

art can be used. Examples of amine protecting groups include, but are not limited to, the following: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl. Also included in the term "amine protecting group" are acyl groups such as azidobenzoyl, p-benzoylbenzoyl, o-benzylbenzoyl, p-acetylbenzoyl, dansyl, glycyl-p-benzoylbenzoyl, phenylbenzoyl, m-benzoylbenzoyl, benzoylbenzoyl.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound of formula (I) is modified by making acid or base salts of the compound of formula (I). Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like.

"Prodrugs" are considered to be any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of the compounds of formula (I) are prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved, either in routine

manipulation or *in vivo*, to the parent compounds. Prodrugs include compounds of formula (I) wherein hydroxy, amine, or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I); and the like.

Pharmaceutically acceptable salts of the compounds of the invention can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

The term "amino acid" as used herein means an organic compound containing both a basic amino group and an acidic carboxyl group. Included within this term are modified and unusual amino acids, such as those disclosed in, for example, Roberts and Vellaccio (1983) The Peptides, 5: 342-429, the teaching of which is hereby incorporated by reference. Modified or unusual amino acids which can be used to practice the invention include, but are not limited to, D-amino acids, hydroxylysine, 4-hydroxyproline, ornithine, 2,4-diaminobutyric acid, homoarginine, norleucine, N-methylaminobutyric acid, naphthylalanine, phenylglycine, ß-phenylproline, tert-leucine, 4-aminocyclohexylalanine, N-methyl-norleucine, 3,4-dehydroproline, 4-aminopiperidine-4-carboxylic acid,

6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopropanecarboxylic acid, and 2-benzyl-5-aminopentanoic acid.

The term "amino acid residue" as used herein means that portion of an amino acid (as defined herein) that is present in a peptide.

The term "peptide" as used herein means a linear compound that consists of two or more amino acids (as defined herein) that are linked by means of a peptide bond. The term "peptide" also includes compounds containing both peptide and non-peptide components, such as pseudopeptide or peptide mimetic residues or other non-amino acid components. Such a compound containing both peptide and non-peptide components may also be referred to as a "peptide analog".

A "pseudopeptide" or "peptide mimetic" is a compound which mimics the structure of an amino acid residue or a peptide, for example, by using linking groups other than amide linkages between the peptide mimetic and an amino acid residue (pseudopeptide bonds) and/or by using non-amino acid substituents and/or a modified amino acid residue.

A "pseudopeptide residue" means that portion of an pseudopeptide or peptide mimetic (as defined herein) that is present in a peptide.

The term "peptide bond" means a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of one amino acid and the amino group of a second amino acid.

The term "pseudopeptide bonds" includes peptide bond isosteres which may be used in place of or as substitutes for the normal amide linkage. These substitute or amide "equivalent" linkages are formed from combinations of atoms not normally found in

peptides or proteins which mimic the spatial requirements of the amide bond and which should stabilize the molecule to enzymatic degradation.

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. Preferred methods include but are not limited to those methods described below.

The following abbreviations are used herein:

D-Abu	D-2-aminobutyric acid
β-Ala, b-Ala or βAla	3-aminopropionic acid
Boc	t-butyloxycarbonyl
Boc-iodo-Mamb	t-butyloxycarbonyl-3-aminomethyl-4-iodo-benzoic acid
Boc-Mamb	t-butyloxycarbonyl-3-aminomethylbenzoic acid
Boc-ON	[2-(tert-butyloxycarbonyloxylimino)-2-phenylacetonitrile
Cl_2Bzl	dichlorobenzyl
CBZ or Cbz	Carbobenzyloxy
DCC	dicyclohexylcarbodiimide
DIEA	diisopropylethylamine
di-NMeOrn	N-αMe-N-γMe-ornithine
DMAP	4-dimethylaminopyridine
HBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
NMeArg or MeArg	α-N-methyl arginine
NMeAmf	N-Methylaminomethylphenylalanine
NMeAsp	α-N-methyl aspartic acid
NMeGly or MeGly	N-methyl glycine

NMe-Mamb	N-methyl-3-aminomethylbenzoic acid
NMM	N-methylmorpholine
OcHex	O-cyclohexyl
OBzl	O-benzyl
TBTU	2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
Tos	tosyl

The following conventional three-letter amino acid abbreviations are used herein; the conventional one-letter amino acid abbreviations are not used herein:

Ala	=	alanine
Arg	=	arginine
Asn	=	asparagine
Asp	=	aspartic acid
Cys	=	cysteine
Gln	=	glutamine
Glu	=	glutamic acid
Gly	=	glycine
His	=	histidine
Ile	=	isoleucine
Leu	=	leucine
Lys	=	lysine
Met	=	methionine
Nle	=	norleucine
Phe	=	phenylalanine
Phg	=	phenylglycine
Pro	=	proline
Ser	=	serine
Thr	=	threonine
Trp	=	tryptophan
Tyr	=	tyrosine
Val	=	valine

Peptide Synthesis

The compounds of the present invention can be synthesized using standard synthetic methods known to those skilled in the art. Preferred methods include but are not limited to those methods described below.

Generally, peptides are elongated by deprotecting the α-amine of the C-terminal residue and coupling the next suitably protected amino acid through a peptide linkage using the methods described. This deprotection and coupling procedure is repeated until the desired sequence is obtained. This coupling can be performed with the constituent amino acids in a stepwise fashion, or condensation of fragments (two to several amino acids), or combination of both processes, or by solid phase peptide synthesis according to the method originally described by Merrifield, J. Am. Chem. Soc., 85, 2149-2154 (1963), the disclosure of which is hereby incorporated by reference.

The compounds of the invention may also be synthesized using automated peptide synthesizing equipment. In addition to the foregoing, procedures for peptide synthesis are described in Stewart and Young, "Solid Phase Peptide Synthesis", 2nd ed, Pierce Chemical Co., Rockford, IL (1984); Gross, Meienhofer, Udenfriend, Eds., "The Peptides: Analysis, Synthesis, Biology, Vol. 1, 2, 3, 5, and 9, Academic Press, New York, (1980-1987); Bodanszky, "Peptide Chemistry: A Practical Textbook", Springer-Verlag, New York (1988); and Bodanszky et al. "The Practice of Peptide Sythesis" Springer-Verlag, New York (1984), the disclosures of which are hereby incorporated by reference.

The coupling between two amino acid derivatives, an amino acid and a peptide, two peptide fragments, or the cyclization of a peptide can be carried out using standard coupling procedures such as the azide method, mixed carbonic acid anhydride (isobutyl chloroformate)

method, carbodiimide (dicyclohexylcarbodiimide, diisopropylcarbodiimide, or water-soluble carbodiimides) method, active ester (p-nitrophenyl ester, N-hydroxysuccinic imido ester) method, Woodward reagent K method, carbonyldiimidazole method, phosphorus reagents such as BOP-Cl, or oxidation-reduction method. Some of these methods (especially the carbodiimide) can be enhanced by the addition of 1-hydroxybenzotriazole. These coupling reactions may be performed in either solution (liquid phase) or solid phase.

The functional groups of the constituent amino acids must be protected during the coupling reactions to avoid undesired bonds being formed. The protecting groups that can be used are listed in Greene, "Protective Groups in Organic Synthesis" John Wiley & Sons, New York (1981) and "The Peptides: Analysis, Sythesis, Biology, Vol. 3, Academic Press, New York (1981), the disclosure of which is hereby incorporated by reference.

The α-carboxyl group of the C-terminal residue is usually protected by an ester that can be cleaved to give the carboxylic acid. These protecting groups include: 1) alkyl esters such as methyl and t-butyl, 2) aryl esters such as benzyl and substituted benzyl, or 3) esters which can be cleaved by mild base treatment or mild reductive means such as trichloroethyl and phenacyl esters. In the solid phase case, the C-terminal amino acid is attached to an insoluble carrier (usually polystyrene). These insoluble carriers contain a group which will react with the carboxyl group to form a bond which is stable to the elongation conditions but readily cleaved later. Examples of which are: oxime resin (DeGrado and Kaiser (1980) *J. Org. Chem.* **45**, 1295-1300) chloro or bromomethyl resin, hydroxymethyl resin, and aminomethyl resin. Many of these resins are

commercially available with the desired C-terminal amino acid already incorporated.

The α-amino group of each amino acid must be protected. Any protecting group known in the art can be used. Examples of these are: 1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; 2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); 3) aliphatic carbamate types such as tert-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; 4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; 5) alkyl types such as triphenylmethyl and benzyl; 6) trialkylsilane such as trimethylsilane; and 7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl. The preferred α-amino protecting group is either Boc or Fmoc. Many amino acid derivatives suitably protected for peptide synthesis are commercially available.

The α-amino protecting group is cleaved prior to the coupling of the next amino acid. When the Boc group is used, the methods of choice are trifluoroacetic acid, neat or in dichloromethane, or HCl in dioxane. The resulting ammonium salt is then neutralized either prior to the coupling or in situ with basic solutions such as aqueous buffers, or tertiary amines in dichloromethane or dimethylformamide. When the Fmoc group is used, the reagents of choice are piperidine or substituted piperidines in dimethylformamide, but any secondary amine or aqueous basic solutions can be used. The deprotection is carried out at a temperature between 0 °C and room temperature.

Any of the amino acids bearing side chain functionalities must be protected during the preparation of the peptide using any of the above-identified groups. Those skilled in the art will appreciate that the selection and use of appropriate protecting groups for these side chain functionalities will depend upon the amino acid and presence of other protecting groups in the peptide. The selection of such a protecting group is important in that it must not be removed during the deprotection and coupling of the α-amino group.

For example, when Boc is chosen for the α-amine protection the following protecting groups are acceptable: *p*-toluenesulfonyl (tosyl) moieties and nitro for arginine; benzyloxycarbonyl, substituted benzyloxycarbonyls, or tosyl for lysine; benzyl or alkyl esters such as cyclopentyl for glutamic and aspartic acids; benzyl ethers for serine and threonine; benzyl ethers, substituted benzyl ethers or 2-bromobenzyloxycarbonyl for tyrosine; *p*-methylbenzyl, *p*-methoxybenzyl, acetamidomethyl, benzyl, or t-butylsulfonyl for cysteine; and the indole of tryptophan can either be left unprotected or protected with a formyl group.

When Fmoc is chosen for the α-amine protection usually tert-butyl based protecting groups are acceptable. For instance, Boc can be used for lysine, tert-butyl ether for serine, threonine and tyrosine, and tert-butyl ester for glutamic and aspartic acids.

Once the elongation and cyclization of the peptide is completed all of the protecting groups are removed. For the liquid phase synthesis the protecting groups are removed in whatever manner as dictated by the choice of protecting groups. These procedures are well known to those skilled in the art.

When a solid phase synthesis is used, the peptide should be removed from the resin without simultaneously

removing protecting groups from functional groups that might interfere with the cyclization process. Thus, if the peptide is to be cyclized in solution, the cleavage conditions need to be chosen such that a free α-carboxylate and a free α-amino group are generated without simultaneously removing other protecting groups. Alternatively, the peptide may be removed from the resin by hydrazinolysis, and then coupled by the azide method. Another very convenient method involves the synthesis of peptides on an oxime resin, followed by intramolecular nucleophilic displacement from the resin, which generates a cyclic peptide (Osapay, Profit, and Taylor (1990) *Tetrahedron Letters* **43**, 6121-6124). When the oxime resin is employed, the Boc protection scheme is generally chosen. Then, the preferred method for removing side chain protecting groups generally involves treatment with anhydrous HF containing additives such as dimethyl sulfide, anisole, thioanisole, or p-cresol at 0 °C. The cleavage of the peptide can also be accomplished by other acid reagents such as trifluoromethanesulfonic acid/trifluoroacetic acid mixtures.

Unusual amino acids used in this invention can be synthesized by standard methods familiar to those skilled in the art ("The Peptides: Analysis, Sythesis, Biology, Vol. 5, pp. 342-449, Academic Press, New York (1981)). N-Alkyl amino acids can be prepared using procedures described in previously (Cheung et al., (1977) *Can. J. Chem.* **55**, 906; Freidinger et al., (1982) *J. Org. Chem.* **48**, 77 (1982)), which are incorporated here by reference.

The compounds of the present invention may be prepared using the procedures further detailed below as well as the procedures described in PCT Patent Application International Publication Number

WO 93/07170, the disclosure of which is hereby incorporated herein by reference. Those compounds referred to by Example Number which are not detailed herein are disclosed in detail in PCT International Publication Number WO 93/07170.

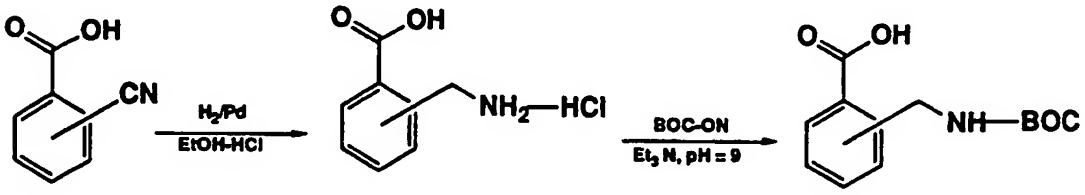
Representative materials and methods that may be used in preparing the compounds of the invention are described further below.

Manual solid phase peptide synthesis was performed in 25 mL polypropylene filtration tubes purchased from BioRad Inc. Oxime resin (substitution level = 0.96 mmol/g) was prepared according to published procedures (DeGrado and Kaiser (1980) *J. Org. Chem.* **45**, 1295). All chemicals and solvents (reagent grade) were used as supplied from the vendors cited without further purification. t-Butyloxycarbonyl (Boc) amino acids and other starting amino acids may be obtained commercially from Bachem Inc., Bachem Biosciences Inc. (Philadelphia, PA), Advanced ChemTech (Louisville, KY), Peninsula Laboratories (Belmont, CA), or Sigma (St. Louis, MO). 2-(1H-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and TBTU were purchased from Advanced ChemTech. N-methylmorpholine (NMM), *m*-cresol, D-2-aminobutyric acid (Abu), trimethylacetylchloride, diisopropylethylamine (DIEA), 3-cyanobenzoic acid and [2-(tert-butyloxycarbonyloxylimino)-phenylacetonitrile] (Boc-ON) were purchased from Aldrich Chemical Company. Dimethylformamide (DMF), ethyl acetate, chloroform ($CHCl_3$), methanol (MeOH), pyridine and hydrochloric acid (HCl) were obtained from Baker. Acetonitrile, dichloromethane (DCM), acetic acid (HOAc), trifluoroacetic acid (TFA), ethyl ether, triethylamine, acetone, and magnesium sulfate were purchased from EM Science. Palladium on carbon catalyst (10% Pd) was purchased from Fluka Chemical Company. Absolute ethanol was obtained from Quantum Chemical Corporation. Thin

layer chromatography (TLC) was performed on Silica Gel 60 F_{254} TLC plates (layer thickness 0.2 mm) which were purchased from EM Separations. TLC visualization was accomplished using UV light, iodine, and/or ninhydrin spray. Melting points were determined using a Thomas Hoover or Electrothermal 9200 melting point apparatus and are uncorrected. HPLC analyses were performed on either a Hewlett Packard 1090, Waters Delta Prep 3000, Rainin, or DuPont 8800 system. NMR spectra were recorded on a 300 MHz General Electric QE-300, Varian 300, or Varian 400 spectrometer. Fast atom bombardment mass spectrometry (FAB-MS) was performed on a VG Zab-E double-focusing mass spectrometer using a Xenon FAB gun as the ion source or a Finnigan MAT 8230.

Synthesis of 3 and 4-substituted Boc-aminomethylbenzoic Acid Derivatives

3 and 4-substituted Boc-aminomethylbenzoic acid derivatives useful as intermediates in the synthesis of the compounds of the invention are prepared using standard procedures, for example, as described in *Tett. Lett.*, 4393 (1975); *Modern Synthetic Reactions*, H.O. House (1972); or Harting et al. *J. Am. Chem. Soc.*, 50: 3370 (1928), and as shown schematically below.



3-Aminomethylbenzoic acid•HCl

3-Cyanobenzoic acid (10.0 g, 68 mmol) was dissolved in 200 ml ethanol by heating in a 35-50°C water bath.

Concentrated HCl (6.12 ml, 73 mmol) was added and the solution was transferred to a 500 ml nitrogen-flushed round bottom flask containing palladium on carbon catalyst (1.05 g, 10% Pd/C). The suspension was stirred under an atmosphere of hydrogen for 38 hours, filtered through a scintered glass funnel, and washed thoroughly with H_2O. The ethanol was removed under reduced pressure and the remaining aqueous layer, which contained a white solid, was diluted to 250 ml with additional H_2O. Ethyl ether (250 ml) was added and the suspension was transferred to a separatory funnel. Upon vigorous shaking, all solids dissolved and the aqueous layer was then washed two times with ether, evaporated under reduced pressure to a volume of 150 ml, and lyophilized to give the title compound (3-aminomethylbenzoic acid·HCl) (8.10 g, 64%) as a beige solid. ^1H NMR (D_2O) 4.27 (s, 2H), 7.60 (t, 1H), 7.72 (d,1H), 8.06 (d, 2H).

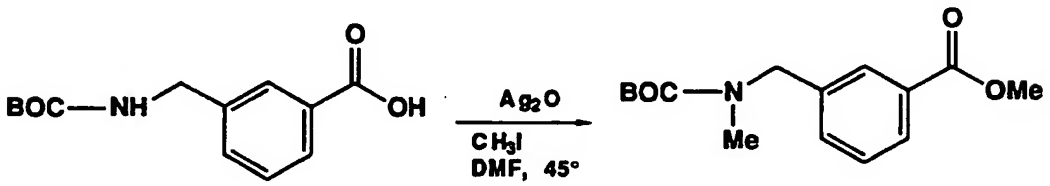
t-Butyloxycarbonyl-3-aminomethylbenzoic Acid (Boc-Mamb)

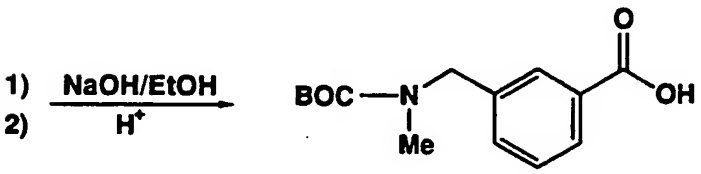
The title compound was prepared according to a modification of standard procedures previously reported in the literature (Itoh, Hagiwara, and Kamiya (1975) *Tett. Lett.*, 4393). 3-Aminomethylbenzoic acid (hydrochloride salt) (3.0 g, 16.0 mmol) was dissolved in 60 ml H_2O. To this was added a solution of Boc-ON (4.33 g, 17.6 mmol) in 60 ml acetone followed by triethylamine (5.56 ml, 39.9 mmol). The solution turned yellow and the pH was adjusted to 9 (wet pH paper) by adding an additional 1.0 ml (7.2 mmol) triethylamine. The solution was stirred overnight at room temperature at which time the acetone was removed under reduced pressure and the remaining aqueous layer was washed three times with ether. The aqueous layer was then acidified to pH 2 with 2N HCl and then

extracted three times with ethyl acetate. The combined organic layers were washed three times with H_2O, dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure. The material was recrystallized from ethyl acetate/ hexane to give two crops of the title compound (2.58 g, 64%) as an off-white solid. mp 123-125°C ; ^1H NMR ($CDCl_3$) 1.47 (s, 9 H), 4.38 (br s, 2 H), 4.95 (br s, 1H), 7.45 (t, 1H), 7.55 (d, 1H), 8.02 (d, 2H).

t-Butyloxycarbonyl-N-methyl-3-aminomethylbenzoic Acid (Boc-NMeMamb)

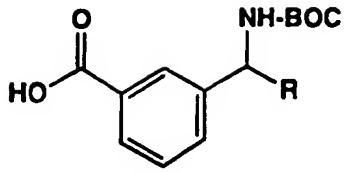
The title compound can be prepared according to standard procedures, for examples, as disclosed in Olsen, *J. Org. Chem.* (1970) 35: 1912), and as shown schematically below.





Synthesis of Aminomethylbenzoic Acid Analogs

Intermediates of the formula below may be prepared using standard synthetic procedures, for example, as shown in the indicated reaction schemes shown below.

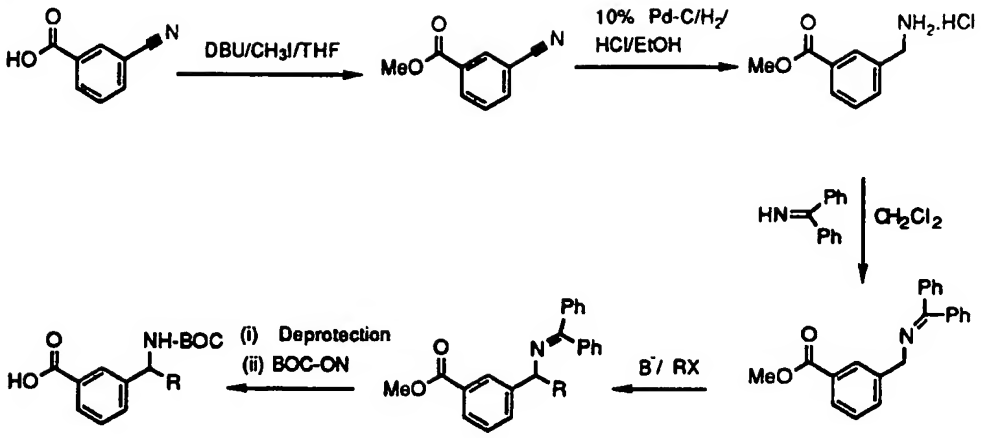


For R = CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, $CH(CH_3)_2$, $C(CH_3)_3$, $CH(CH_3)CH_2CH_3$, benzyl, cyclopentyl, cyclohexyl; see Scheme 1.

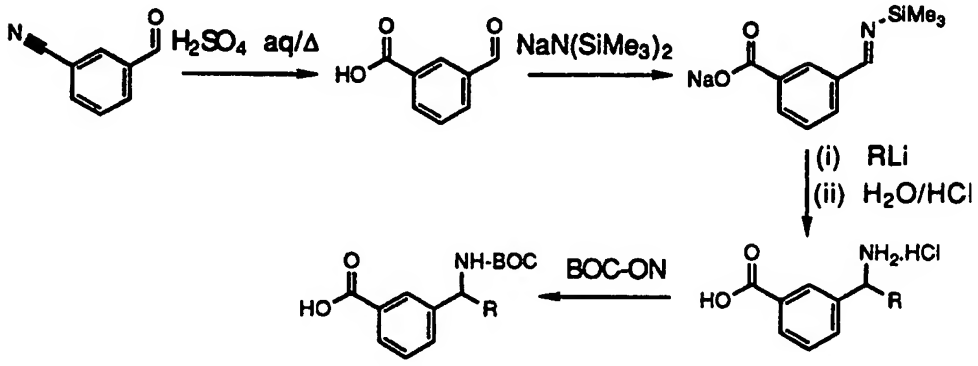
For R = CH_3, $CH_2CH_2CH_2CH_3$, phenyl; see Scheme 2.

For R = CH_3, phenyl; see Scheme 3 and 4.

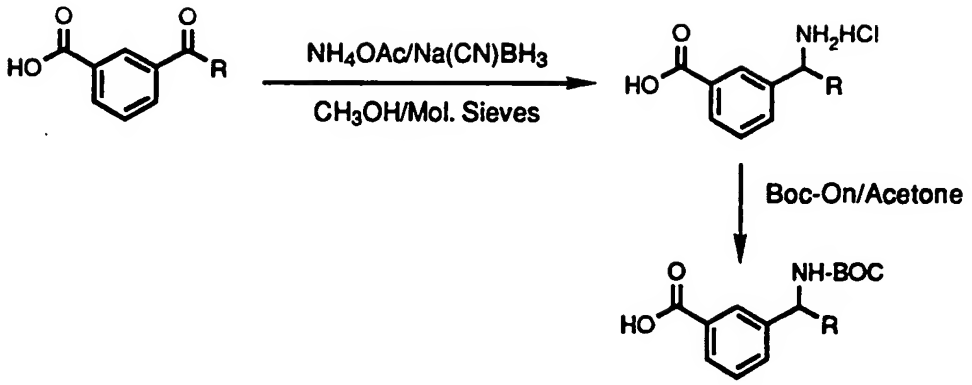
Scheme 1:



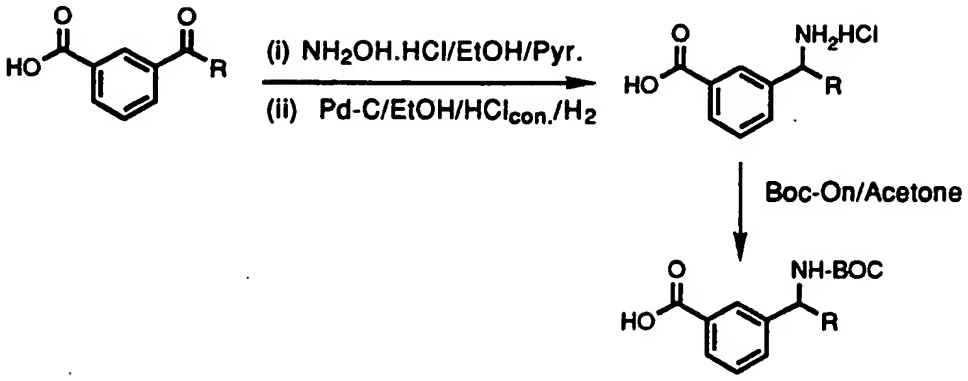
Scheme 2:



Scheme 3:



Scheme 4:



3-[1'-(t-butyloxycarbonyl)aminolethylbenzoic acid (BOC-MeMAMB)

The title compound for the purpose of this invention was prepared according to the Scheme 4 (above).

3-Acetylbenzoic acid (0.50 g, 3 mmol), hydroxylamine hydrochloride (0.70 g, 10 mmol) and pyridine (0.70 ml, 9 mmol) were refluxed in 10 ml ethanol, for 2 h. Reaction mixture was concentrated, residue triturated with water, filtered and dried. Oxime was isolated as a white solid (0.51 g ; 94.4% yield).

^{1}HNMR (CD_3OD) 7.45-8.30(m, 4H), 2.30(s, 3H). MS (CH_4-CI) [M+H-O] = 164.

A solution of the oxime (0.51 g, 3 mmol) in ethanol, containing 10% Pd on carbon (1.5 g) and conc. HCl (0.25 ml, 3 mmol) was hydrogenated at 30 psi H_2 pressure in a Parr hydrogenator for 5 h. Catalyst was filtered and the filtrate concentrated. Residue was triturated with ether. Amine hydrochloride was isolated as a white solid (0.48 g ; 85.7% yield). ^{1}HNMR (CD_3OD) 7.6-8.15(m, 4H), 4.55(q, 1H), 1.70(s, 3H). MS [M+H] = 166.

Amine hydrochloride (0.40 g, 2 mmol) was dissolved in 15 ml water. A solution of BOC-ON (0.52 g, 2.1 mmol) in 15 ml acetone was added, followed by the addition of triethylamine (0.8 ml, 6 mmol). Reaction was allowed to proceed for 20 h. Reaction mixture was concentrated, partitioned between ethyl acetate and water. Aqueous layer was acidified to pH 2 using 10% HCl solution. Product was extracted in ethyl acetate, which after the usual work up and recrystallization from ethyl acetate/hexane, gave the title compound as a white solid (0.30 g ; 57% yield). m.p. 116-118° C.
^{1}HNMR ($CDCl_3$) 7.35-8.2(m, 4H), 4.6(bs, 1.5H), 1.50(d, 3H), 1.40(s, 9H). MS (NH_3-CI) [M+NH_4] = 283.

3-[1'-(t-butyloxycarbonyl)aminolbenzylbenzoic acid (BOC-PhMAMB)

The title compound for the purpose of this invention was prepared according to the Scheme 4 (above), by the procedure similar to that for the methyl derivative.

A solution of 3-benzoylbenzoic acid (2.00 g, 9 mmol), hydroxylamine hydrochloride (2.00 g, 29 mmol) and pyridine (2.00 ml, 25 mmol) in ethanol was refluxed for 12 h. After the usual extractive work up, white solid

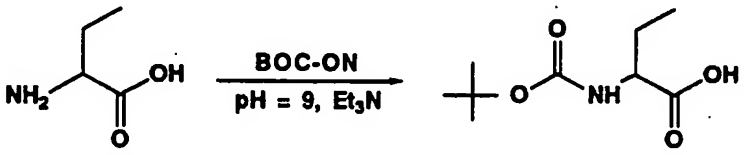
was obtained (2.41 g). The product still contained traces of pyridine, but was used in the next step without further purification.

The crude product (2.00 g, ~8 mmol) was dissolved in 200 ml ethanol. 10% Pd-C (2.00 g) and con. HCl (1.3 ml, 16 mmol) were added. Reaction mixture was hydrogenated at 30 psi for 1 h. The catalyst was filtered and the reaction mixture concentrated. Upon trituration of the residue with ether and drying under vacuum, amine hydrochloride was obtained as a white solid (2.12 g ; 97% yield). ^{1}HNMR (CD_3OD) 7.4-8.15(m, 10H), 5.75(s, 1H). MS (CH_4-CI) [M+H-OH] = 211.

Amine hydrochloride (1.00 g, 4 mmol) was converted to its BOC-derivative by a procedure similar to the methyl case. 0.60 g (48% yield) of the recrystallized (from ethanol/hexane) title compound was obtained as a white solid. m.p. 190-192° C. ^{1}HNMR (CD_3OD) 7.2-8.0(m, 10H), 5.90 (2s, 1H, 2 isomers), 1.40(s, 9H). MS (NH_3-CI) [M+NH_4-C_4H_8] = 289

t-Butyloxycarbonyl-D-2-aminobutyric Acid

The title compound was prepared by a modification of procedures previously reported in the literature (Itoh, Hagiwara, and Kamiya (1975) *Tett. Lett.*, 4393), as shown in the scheme below.



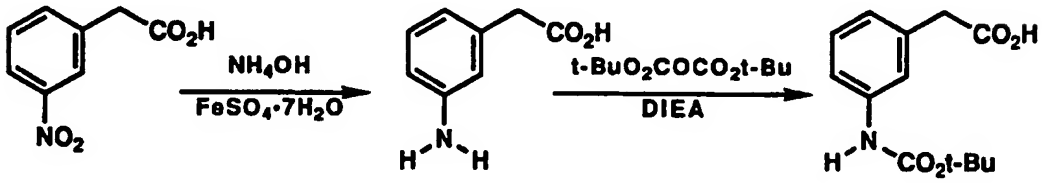
D-2-aminobutyric acid

D-2-aminobutyric acid (1.0 g, 9.70 mmol) was dissolved in 20 ml H_2O and a solution of Boc-ON (2.62 g, 10.6 mmol) in 20 ml acetone was added. A white precipitate formed which dissolved upon addition of

triethylamine (3.37 ml, 24.2 mmol) to give a pale yellow solution (pH = 9, wet pH paper). The solution was stirred at room temperature overnight at which time the acetone was removed under reduced pressure. The remaining aqueous layer was extracted with ether three times, acidified to pH 2 with concentrated HCl, and then extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give t-butyloxycarbonyl-D-2-aminobutyric acid as an oil (2.05 g,greater than quantitative yield, contains solvent), which was used without further purification. ^{1}H NMR ($CDCl_3$) 0.98 (t, 3H), 1.45 (s, 9H), 1.73 (m, 1H), 1.90 (m, 1H), 4.29 (m, 1H), 5.05 (m, 1H).

Synthesis of t-Butyloxycarbonyl-3-aminophenylacetic Acid

t-Butyloxycarbonyl-3-aminophenylacetic acids useful as intermediates in the synthesis of the compounds of the invention are prepared using standard procedures, for example, as described in Collman and Groh (1982) *J. Am. Chem. Soc.*, 104: 1391, and as shown schematically below.



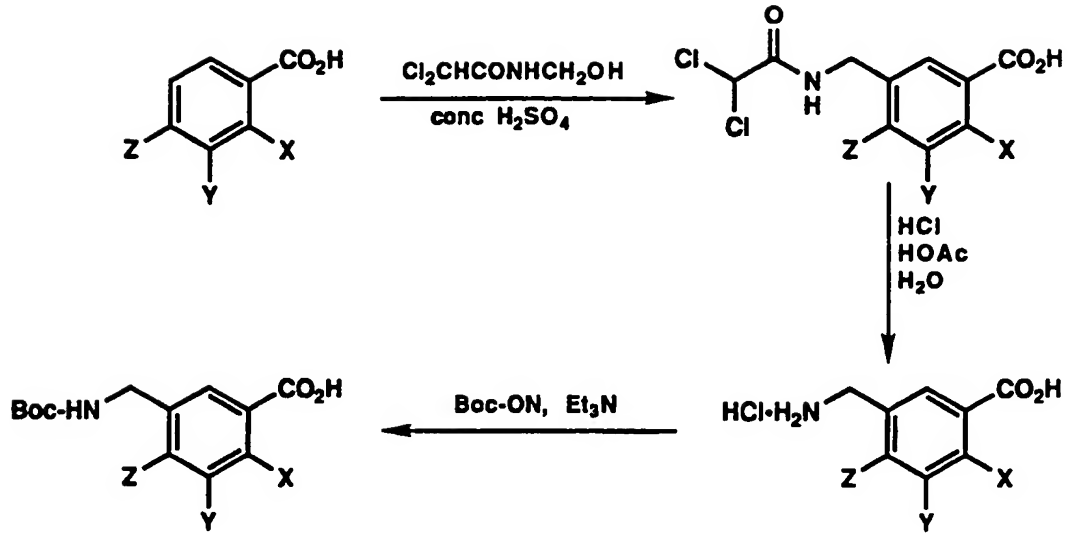
t-Butyloxycarbonyl-3-aminophenylacetic Acid

A solution of 3-aminophenylacetic acid (Aldrich, 10 g, 66 mmol), di-*tert*-butyl dicarbonate (15.8 g, 72 mmol), and DIEA (8.6 g, 66 mmol) in 50 ml of dichloromethane was stirred overnight at room

temperature. The reaction mixture was concentrated, partitioned between dichloromethane-H_2O, the water layer was separated, acidified to pH 3 with 1N HCl, and extracted with dichloromethane. The extracts were washed with H_2O, brine, dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure. This material was purified by recrystallization from heptane to provide the title compound (3.7 g, 22%) as a white solid. mp 105°C; ^1H NMR ($CDCl_3$) 7.35 (s, 1H), 7.25 (m, 3H), 6.95 (m, 1H), 6.60 (br s, 1H), 3.65 (s, 2H), 1.50 (s, 9H).

Synthesis of 4, 5, and 6-Substituted 3-Aminomethylbenzoic Acid•HCl, and 4, 5, and 6-Substituted t-Butyloxycarbonyl-3-aminomethylbenzoic Acid Derivatives

4, 5, and 6-Substituted 3-aminomethylbenzoic acid•HCl, and 4, 5, and 6-substituted t-butyloxycarbonyl-3-aminomethylbenzoic acid derivatives useful as intermediates in the synthesis of the compounds of the invention are prepared using standard procedures, for example, as described in Felder et al *Helv. Chim. Acta*, 48: 259 (1965); de Diesbach *Helv. Chim. Acta*, 23: 1232 (1949); Truitt and Creagn *J. Org. Chem.*, 27: 1066 (1962); or Sekiya et al *Chem. Pharm. Bull.*, 11: 551 (1963), and as shown schematically below.



Synthesis of 4-Chloro-3-aminomethylbenzoic Acid•HCl

The title compound was prepared by modification of procedures previously reported in the literature (Felder et al (1965) *Helv. Chim. Acta*, 48: 259). To a solution of 4-chlorobenzoic acid (15.7 g, 100 mmol) in 150 ml of concentrated sulfuric acid was added N-hydroxymethyl dichloroacetamide (23.7 g, 150 mmol) in portions. The reaction mixture was stirred at room temperature for 2 days, poured onto 375 g of ice, stirred for 1 hour, the solid was collected by filtration, and washed with H_2O. The moist solid was dissolved in 5% sodium bicarbonate solution, filtered, and acidified to pH 1 with concentrated HCl. The solid was collected by filtration, washed with H_2O, and air-dryed overnight to give 4-chloro-3-dichloroacetylaminomethylbenzoic acid (26.2 g, 89%) as a white powder.

A suspension of 4-chloro-3-dichloroacetylaminomethylbenzoic acid (26.2 g, 88 mmol) in 45 ml of acetic acid, 150 ml of concentrated HCl, and

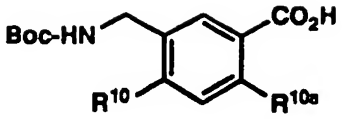
150 ml of H_2O was heated to reflux for 3 hours, filtered while hot, and allowed to cool to room temperature. The solid was collected by filtration, washed with ether, washed with acetone-ether, and air-dryed overnight to give the title compound (7.6 g, 39%) as off-white crystals. mp 278-9°C; ^1H NMR (D_6-DMSO) 13.40 (br s, 1H), 8.75 (br s, 3H), 8.20 (s, 1H), 7.95 (dd, 1H), 7.70 (d, 1H), 4.20 (br s, 2H).

t-Butyloxycarbonyl-4-chloro-3-aminomethylbenzoic Acid

A suspension of 4-chloro-3-aminomethylbenzoic acid•HCl (6.7 g, 30 mmol) and triethylamine (9.3 g, 92 mmol) in 50 ml of H_2O, was added to a solution of Boc-ON (9.2 g, 38 mmol) in 50 ml of tetrahydrofuran cooled to 0°C. The reaction mixture was stirred at room temperature overnight, and the volatile compounds were removed by concentration under reduced pressure. The residue was diluted with H_2O, washed with ether, acidified to pH 3 with 1N HCl, and extracted with ethyl acetate. The extracts were washed with H_2O, brine, dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure. This material was triturated with ether-hexane to provide the title compound (7.4 g, 87%) as a white powder. mp 159°C (dec); ^1H NMR (D_6-DMSO) 13.20 (br s, 1H), 7.90 (s, 1H), 7.80 (dd, 1H), 7.60 (br s, 1H), 7.55 (d, 1H), 4.20 (br d, 2H), 1.40 (s, 9H).

4 and 6-Substituted t-Butyloxycarbonyl-3-aminomethylbenzoic Acid Derivatives

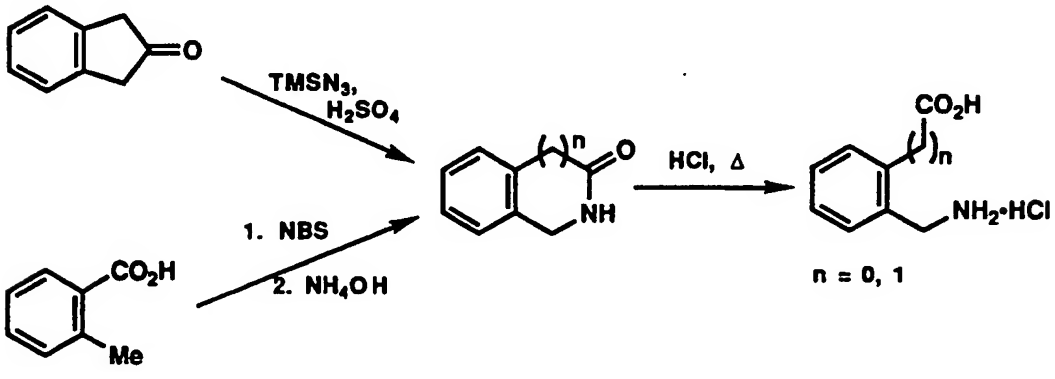
The compounds listed below were prepared using the general procedure described above for t-butyloxycarbonyl-4-chloro-3-aminomethylbenzoic acid.



R^{10a}	R^{10}	mp °C
H	Cl	159
H	I	168
H	Me	155
H	MeO	171
Cl	H	150
I	H	182
Me	H	166
MeO	H	79

Synthesis of 2-Aminomethylbenzoic Acid•HCl and 2-Aminomethylphenylacetic Acid•HCl

2-Aminomethylbenzoic acid·HCl and 2-aminomethylphenylacetic acid·HCl useful as intermediates in the synthesis of the compounds of the invention are prepared using standard procedures, for example, as described in Naito et al *J. Antibiotics*, 30: 698 (1977); or Young and Sweet *J. Am. Chem. Soc.*, 80: 800 (1958), and as shown schematically below.



2-Aminomethylphenylacetic Acid d-Lactam

The title compound was prepared by modification of procedures previously reported in the literature (Naito et al. (1977) *J. Antibiotics*, 30: 698). To an ice-cooled suspension of 2-indanone (10.8 g, 82 mmol) and azidotrimethylsilane (9.4 g, 82 mmol) in 115 ml of chloroform was added 25 ml of concentrated sulfuric acid at a rate to maintain the temperature between 30-40°C. After an additional 3 hours, the reaction mixture was poured onto ice, and the water layer was made basic with concentrated ammonium hydroxide. The chloroform layer was separated, washed with H_2O, brine, dried over anhydrous magnesium sulfate, and evaporated to dryness under reduced pressure. This material was purified by sublimination (145°C, <1 mm), followed by recrystallization from benzene to give the title compound (5.4 g, 45%) as pale yellow crystals. mp 149-150°C; ^1H NMR ($CDCl_3$) 7.20 (m, 5H), 4.50 (s, 2H), 3.60 (s, 2H).

2-Aminomethylphenylacetic Acid•HCl

The title compound was prepared by modification of procedures previously reported in the literature (Naito et al. (1977) *J. Antibiotics*, 30: 698). A mixture of 2-aminomethylphenylacetic acid d-lactam (6.4 g, 44 mmol) and 21 ml of 6N HCl was heated to reflux for 4 hours. The reaction mixture was treated with activated carbon (Norit A), filtered, evaporated to dryness, and the residual oil triturated with acetone. Filtration provided the title compound (5.5 g, 62%) as colorless crystals. mp 168°C (dec); ^1H NMR (D_6-DMSO) 12.65 (br s, 1H), 8.35 (br s, 3H), 7.50 (m, 1H), 7.35 (m, 3H), 4.05 (ABq, 2H), 3.80 (s, 2H).

2-Aminomethylbenzoic Acid g-Lactam

The title compound was prepared by modification of procedures previously reported in the literature (Danishefsky et al. (1975) *J. Org. Chem.*, 40: 796). A mixture of methyl *o*-toluate (45 g, 33 mol), N-bromosuccinimide (57 g, 32 mol), and dibenzoyl peroxide (0.64 g) in 175 ml of carbon tetrachloride was heated to reflux for 4 hours. The cooled reaction mixture was filtered, evaporated to dryness under reduced pressure, dissolved in 250 ml of methanol, and concentrated ammonium hydroxide (75 ml, 1.11 mol) was added. The reaction mixture was heated to reflux for 5 hours, concentrated, filtered, and the solid washed with H_2O followed by ether. This material was purified by recrystallization from H_2O to give the title compound (11.0 g, 26%) as a white solid. mp 150°C; ^1H NMR ($CDCl_3$) 7.90 (d, 1H), 7.60 (t, 1H), 7.50 (t, 2H), 7.00 (br s, 1H), 4.50 (s, 2H).

2-Aminomethylbenzoic Acid•HCl

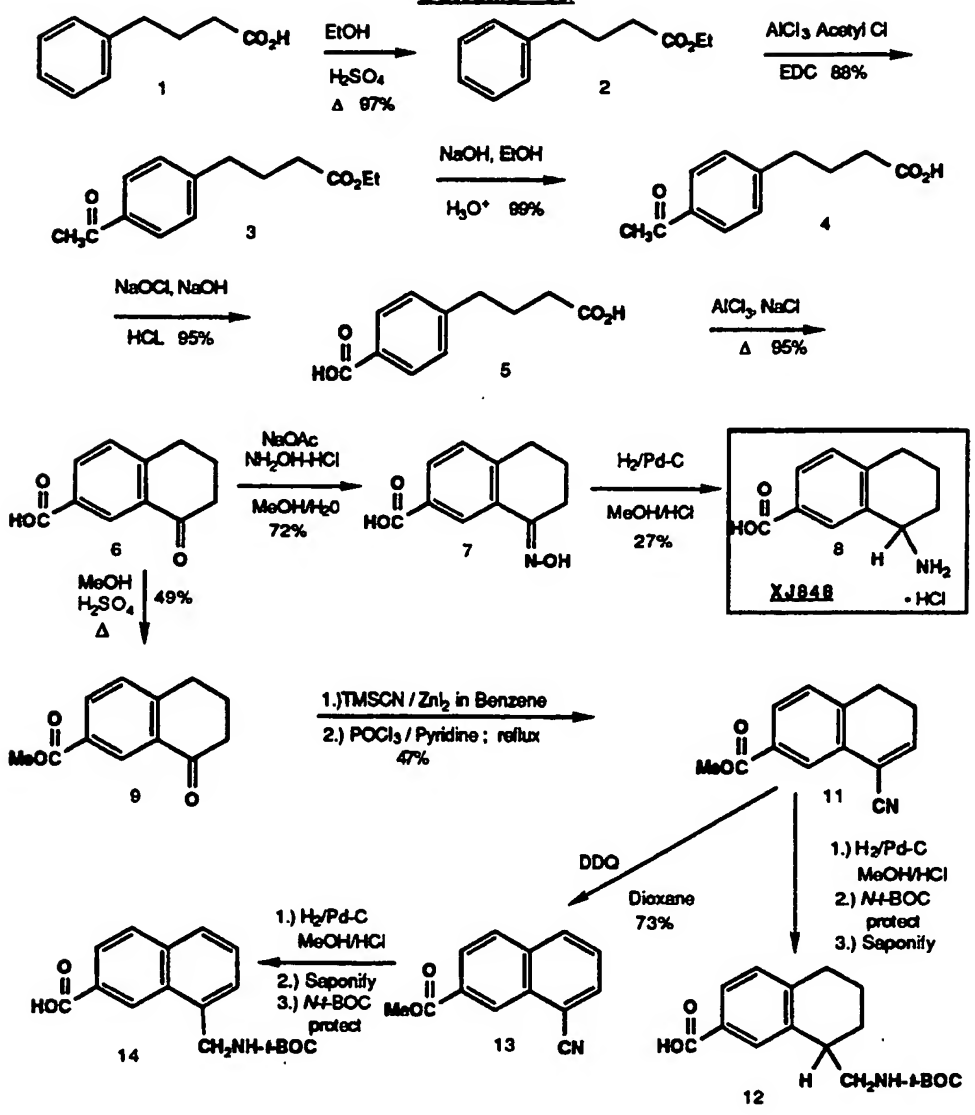
The title compound was prepared using the general procedure described above for 2-aminomethylphenylacetic acid•HCl. The lactam (3.5 g, 26 mmol) was converted to the title compound (2.4 g, 50%) as colorless crystals. mp 233°C (dec); ^1H NMR (D_6-DMSO) 13.40 (br s, 1H), 8.35 (br s, 3H), 8.05 (d, 1H), 7.60 (m, 3H), 4.35 (br s, 2H).

Alternatives to Mamb: Other Cyclic Peptide Intermediates

Alternatives to Mamb useful as carbocylic residues R^{31} in the cyclic peptides of the invention include aminoalkyl-naphthoic acid and aminoalkyl-tetrahydronaphthoic acid residues. Representative aminoalkyl-naphthoic acid and aminoalkyl-tetrahydronaphthoic acid intermediates useful in the synthesis of cyclic peptides of the present invention are

described below. The synthesis of these intermediates is outlined below in Scheme 4a.

Scheme 4a



The title compound was prepared according to a modification of standard procedures previously reported in the literature (Earnest, I., Kalvoda, J., Rihs, G., and Mutter, M., Tett. Lett., Vol. 31, No. 28, pp 4011-4014, 1990).

8-Amino-5,6,7,8-tetrahydro-2-naphthoic Acid Hydrochloride (8)

As shown below in Scheme 4a, 4-phenylbutyric acid (1) was converted to the ethyl ester (2) which was acylated via aluminum chloride and acetylchloride to give 4-acetylphenylbutyric acid ethyl ester (3). This ester was subjected to saponification to give 4-acetylphenylbutyric acid (4). Subsequently, the acetyl group was oxidized to give 4-carboxyphenylbutyric acid (5) which was converted to the 1-tetralin-7-carboxylic acid (6) using aluminum chloride in a Friedel-Crafts cyclization with resonably high yield. At that point, the tetralone was split into two portions and some was converted to the oxime (7) using sodium acetate and hydroxylamine hydrochloride.The oxime was subjected to hydrogenolysis to give the racemic mixture of 8-amino-5,6,7,8-tetrahydro-2-naphthoic acid as the hydrochloride (8) for use as an intermediate for incorporation into the cyclic peptide.

Part A - A solution of 4-phenylbutyric acid (50.0 g, 0.3 mol) in ethanol (140 mL) with concentrated sulfuric acid (0.53 mL) was stirred at reflux over 5 hours. The cooled solution was poured into ice water and extracted with ethyl acetate. The combined organic layers were backwashed with brine, dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give 4-phenylbutyric acid ethyl ester (56.07 g, 0.29 mol, 97%) as a yellow liquid. ^{1}H NMR ($CDCl_3$) d 7.3-7.1 (m, 5H), 4.1 (q, 2H, J=7.1 Hz), 2.7 (t, 2H, J=7.7 Hz), 2.3 (t, 2H, J=7.5 Hz), 1.95 (quintet, 2H, J=7.5 Hz), 1.25 (t, 3H, J=7.1 Hz).

Part B - To a solution of aluminum chloride (153 g, 1.15 mol), and acetyl chloride (38.5 mL, 42.5 g, 0.54 mol) in

dichloromethane (1500 mL) was added, dropwise, a solution of 4-phenylbutyric acid ethyl ester (50.0 g, 0.26 mol) in dichloromethane (500 mL). All was stirred at ambient temperature for 15 minutes. The solution was poured into cold concentrated hydrochloric acid (2000 mL) and then extracted with dichloromethane. The combined organic layers were backwashed with brine, dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give 4-acetylphenylbutyric acid ethyl ester (53.23 g, 0.23 mol, 88%) as a dark yellow liquid. ^{1}H NMR ($CDCl_3$) d 7.9 (d, 2H, J=8.1 Hz), 7.25 (d, 2H, J=8.4 Hz), 4.1 (q, 2H, J=7.1 Hz), 2.75 (t, 2H, J=7.6 Hz), 2.6 (s, 3H), 2.35 (t, 2H, J=7.6 Hz), 2.0 (quintet, 2H, J=7.5 Hz), 1.25 (t, 3H, J=7.1 Hz).

Part C -To a solution of 4-acetylphenylbutyric acid ethyl ester (50.0 g, 0.21 mol) in ethanol (1250 mL) was added, dropwise, a solution of sodium hydroxide (50.0 g) in water (1250 mL). All was stirred at reflux over 4 hours. The solution was concentrated to half volume and then acidified to a pH equal to 1.0 using hydrochloric acid (1N). The resulting precipitate was collected and washed with water to give 4-acetylphenylbutyric acid (53.76 g, 0.26 mol, 99%) as a white solid. mp = 50-52°C; ^{1}H NMR ($CDCl_3$) d 7.9 (d, 2H, J=8.1 Hz), 7.25 (d, 2H, J=9.1 Hz), 2.75 (t, 2H, J=7.7 Hz), 2.6 (s, 3H), 2.4 (t, 2H, J=7.3 Hz), 2.0 (quintet, 2H, J=7.4 Hz).

Part D -To a solution of sodium hypochlorite (330 mL, 17.32 g, 0.234 mol) in a solution of sodium hydroxide (50%, 172 mL), warmed to 55°C, was added, portionwise as a solid, 4-acetylphenylbutyric acid (16.0 g, 0.078 mol) while keeping the temperature between 60-70°C. All was stirred at 55°C over 20 hours. The cooled solution was quenched by the dropwise addition of a solution of

sodium bisulfite (25%, 330 mL). The mixture was then transferred to a beaker and acidified by the careful addition of concentrated hydrochloric acid. The resulting solid was collected, washed with water and dried, then triturated sequentially with chlorobutane and hexane to give 4-carboxyphenylbutyric acid (15.31 g, 0.074 mol, 95%) as a white solid. mp = 190-195°C; ^{1}H NMR (DMSO) d 12.55 (bs, 1H), 8.1 (s, 1H), 7.85 (d, 2H, J=8.1 Hz), 7.3 (d, 2H, J=8.1 Hz), 2.7 (t, 2H, J=7.5 Hz), 2.2 (t, 2H, J=7.4 Hz), 1.8 (quintet, 2H, J=7.5 Hz).

Part E - A mixture of 4-carboxyphenylbutyric acid (10.40 g, 0.05 mol), aluminum chloride (33.34 g, 0.25 mol) and sodium chloride (2.90 g, 0.05 mol) was heated with continual stirring to 190°C over 30 minutes. As the mixture cooled to 60°C, cold hydrochloric acid (1N, 250 mL) was carefully added. The mixture was extracted with dichloromethane. The combined organic layers were backwashed with dilute hydrochloric acid and water, dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The resulting solid was triturated with chlorobutane to give 1-tetralon-7-carboxylic acid (9.59 g, 0.05 mol, 100%) as a brown solid. mp = 210-215°C; ^{1}H NMR (DMSO) d 8.4 (s, 1H), 8.1 (d, 2H, J=8.0 Hz), 7.5 (d, 1H, J=7.9 Hz), 3.0 (t, 2H, J=6.0 Hz), 2.65 (t, 2H, J=6.6 Hz), 2.1 (quintet, 2H, J=6.3 Hz).

Part F - A solution of 1-tetralon-7-carboxylic acid (1.0 g, 0.0053 mol) and sodium acetate (1.93 g, 0.024 mol) and hydroxylamine hydrochloride (1.11 g, 0.016 mol) in a mixture of methanol and water (1:1, 15 mL) was stirred at reflux over 4 hours. The mixture was cooled and then added was more water (50 mL). The solid was collected, washed with water and dried, then triturated with hexane to give 1-tetralonoxime-7-carboxylic acid (0.78 g,

0.0038 mol, 72%) as a white solid. mp = 205-215°C; ^{1}H NMR (DMSO) d 11.3 (s, 2H), 8.4 (s, 1H), 7.8 (d, 1H, J=7.7 Hz), 7.3 (d, 1H, J=7.7 Hz), 2.8 (t, 2H, J=5.9 Hz), 2.7 (d, 2H, J=6.6 Hz), 1.9-1.7 (m, 2H).

Part G - A mixture of 1-tetralonoxime-7-carboxylic acid (0.75 g, 0.0037 mol) in methanol (25 mL) with concentrated hydrochloric acid (0.54 mL, 0.20 g, 0.0056 mol) and palladium on carbon catalyst (0.10 g, 5% Pd/C) was shaken for 20 hours at ambient temperature under an atmosphere of hydrogen (60 psi). The reaction mixture was filtered over Celite® and washed with methanol. The filtrate was evaporated to dryness under reduced pressure and the residue was purified by flash chromatography using hexane:ethyl acetate::1:1 to give the racemic mixture of 8-amino-5,6,7,8-tetrahydro-2-naphthoic acid hydrochloride (0.225 g, 0.001 mol. 27%) as a white solid. mp = 289-291°C; ^{1}H NMR (DMSO) d 8.55 (bs, 3H), 8.2-8.1 (m, 1H), 7.85-7.8 (m, 1H), 7.35-7.25 (m, 1H), 4.5 (m, 1H), 2.9-2.8 (m, 2H), 2.1-1.9 (m, 3H), 1.85-1.7 (m, 1H).

N-(BOC)-8-Aminomethyl-5,6,7,8-tetrahydro-2-naphthoic Acid (12)

As shown below in Scheme 4a, the remaining tetralone was then converted to the methyl ester (9). Using a procedure from Gregory, G.B. and Johnson, A.L, JOC, 1990, 55, 1479, the tetralone methyl ester (9) was converted, first, to the cyanohydrin by treatment with trimethylsilylcyanide and zinc iodide and then, via the *in situ* dehydration with phosphorous oxychloride in pyridine, to the methyl 8-cyano-5,6-dihydro-2-naphthoate (11). This naphthoate was divided into two portions and some was subjected to hydrogenolysis, N-BOC-protection and saponification to give N-(BOC)-8-aminomethyl-5,6,7,8-tetrahydro-2-naphthoic acid (12) as an intermediate for incorporation into the cyclic peptide.

Part A - A mixture of 1-tetralon-7-carboxylic acid (7.0 g, 0.037 mol) in methanol (13.6 mL, 10.8 g, 0.30 mol) with a catalytic amount of hydrochloriic acid (0.07 mL, 0.12 g, 0.0012 mol) was stirred at reflux over 5 hours. The cooled reaction mixture was poured into ice water and extracted with ethyl acetate. The combined organic layers were backwashed with water and brine, dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The resulting solid was purified by flash chromatography using hexane:ethyl acetate::75:25. The resulting solid was triturated with hexane to give 1-tetralon-7-carboxylic acid methyl ester (3.61 g, 0.018 mol, 49%) as a yellow solid. mp = 170-172°C; ^{1}H NMR ($CDCl_3$) d 8.7 (s, 1H), 8.15 (d, 1H, J=8.1 Hz), 7.35 (d, 1H, J=8.1 Hz), 3.95 (s, 3H), 3.05 (d, 2H, J=6.1 Hz), 2.7 (t, 2H, J=6.4 Hz), 2.15 (quintet, 2H, J=6.2 Hz).

Part B - A solution of 1-tetralon-7-carboxylic acid methyl ester (3.50 g, 0.017 mol), trimethylsilylcyanide (1.98 g, 0.02 mol) and zinc iodide (0.10 g) in benzene (20 mL) was stirred at ambient temperature over 15 hours. Then added, sequentially and dropwise, was pyridine (20 mL) and phosphorous oxychloride (4.0 mL, 6.55 g, 0.0425 mol). The reaction mixture was stirred at reflux over 1 hour then evaporated to dryness under reduced pressure. The residue was taken up in chloroform, backwashed with water, dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give methyl 8-cyano-5,6-dihydro-2-naphthoate (1.70 g, 0.008 mol, 47%) as a yellow solid. mp = 73-75°C; ^{1}H NMR ($CDCl_3$) d 8.0-7.9 (m, 1H), 7.3-7.2 (m, 1H), 6.95 (t, 1H, J=4.8 Hz), 3.95 (s, 3H), 2.9 (t, 2H, J=8.3 Hz), 2.6-2.4 (m, 3H)

Part C - A mixture of methyl 8-cyano-5,6-dihydro-2-naphthoate (0.80 g, 0.0038 mol) in methanol (25 mL) with concentrated hydrochloric acid (0.56 mL) and palladium on carbon catalyst (0.40 g, 5% Pd/C) was shaken for 20 hours at ambient temperature under an atmosphere of hydrogen (50 psi). The reaction mixture was filtered over Celite and washed with methanol. The filtrate was evaporated to dryness under reduced pressure and the residue was triturated with hexane to give the racemic mixture of methyl 8-aminomethyl-5,6,7,8-tetrahydro-2-naphthoate (0.80 g, 0.0037 mol, 97%) as a white solid. mp = 172-179°C; ^{1}H NMR (DMSO) d 8.2-8.0 (m, 4H), 7.9-7.7 (m, 6H), 7.5-7.2 (m, 4H), 3.9-3.8 (m, 7H), 3.3-2.7(m, 10H), 2.0-1.6 (m, 8H).

Part D - A solution of methyl 8-aminomethyl-5,6,7,8-tetrahydro-2-naphthoate (0.78 g, 0.0036 mol) and triethylamine (0.55 mL, 0.40 g, 0.004 mol) in aqueous

tetrahydrofuran (50%, 75 mL) was added, portionwise as a solid, 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (0.99 g, 0.004 mol). All was stirred at ambient temperature over 3 hours. The solution was concentrated to half volume and extracted with diethylether. The aqueous layer was then acidified to a pH of 1.0 using hydrochloric acid (1N) and then extraced with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography using hexane:ethyl acetate::8:2 to give methyl N-(BOC)-8-aminomethyl-5,6,7,8-tetrahydro-2-naphthoate (0.54 g, 0.0017 mol, 47%) as a white solid. mp = 72-80°C; ^{1}H NMR (DMSO) d 13.8 (s, 1H), 7.8-7.65 (m, 3H), 7.6-7.5 (m, 3H), 7.25-7.20 (m, 1H), 7.15-7.05 (m, 1H), 3.9-3.8 (m, 1H), 3.2-2.8 (m, 4H), 1.8-1.6 (m, 3H), 1.4 (s, 6H).

Part E - To a solution of methyl N-(BOC)-8-aminomethyl-5,6,7,8-tetrahydro-2-naphthoate (0.50 g, 0.0016 mol) in ethanol (12.5 mL) was added, dropwise, a solution of sodium hydroxide (0.50 g) in water (12.5 mL). All was stirred a reflux over 4 hours. The reaction mixture was concentrated to half volume and then acidified to a pH equal to 1.0 using hydrochloric acid (1N). The residue was puified by flash chromatography using a gradient of hexane:ethyl acetate::1:1 to ethyl acetate to ethyl acetate: methanol::9:1 to give the racemic mixture of the title compound, N-(BOC)-2-aminomethyl-5,6,7,8-tetrahydro-2-naphthoic acid (0.19 g, 0.00062 mol, 39%) as a white solid. mp = 172-176°C; ^{1}H NMR (DMSO) d 7.8 (s, 1H), 7.65 (d, 1H, J=8.1 Hz), 7.15 (d, 1H, J=8.1 Hz), 7.1-7.0 (m, 1H), 3.2-3.1 (m, 2H), 3.0-2.7 (m, 4H), 1.8-1.6 (m, 4H), 1.4 (s, 9H).

N-(BOC)-8-aminomethyl-2-naphthoic acid (14)

The remaining naphthoate (11) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dioxane to aromatize the adjacent ring to give the methyl 8-cyano-2-naphthoate (13). Then, the nitrile was reduced via hydrogentation and the methyl ester saponified to the carboxylic acid. This acid was then N-BOC-protected to give N-(BOC)-8-aminomethyl-2-naphthoic acid (14) as an intermediate for incorporation into the cyclic peptide.

Part A - A solution of methyl 8-cyano-5,6-dihydro-2-naphthoate (1.0 g, 0.0047 mol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.07 g, 0.0047 mol) in dioxane (50 mL) was stirred at 120°C over 16 hours. The reaction mixture was poured into ice water and extracted with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure. The residue was purified by flash chromatography using ethyl acetate to give methyl 8-cyano-2-naphthoate (0.72 g, 0.0034 mol, 73%) as a tan solid. mp = 178-182°C; ^{1}H NMR ($CDCl_3$) d 8.95 (s, 1H), 8.3-8.2 (m, 1H), 8.15-8.10 (m, 1H), 8.0-7.95 (m, 2H), 7.7-7.6 (m, 1H), 4.05 (s, 1H).

Part B - A mixture of methyl 8-cyano-2-naphthoate (1.0 g, 0.0047 mol) in methanol (35 mL) with concentrated hydrochloric acid (0.69 mL) andpalladium on carbon catalyst (0.20 g, 5% Pd/C) was shaken for 6 hours at ambient temperature under anatmosphere of hydrogen (50 psi). The reaction mixture was filtered over Celite® and washed with methanol. The filtrate was evaporated to dryness under reduced pressure and the residue was triturated with hexane to give methyl 8-aminomethyl-2-

naphthoate (0.76 g, 0.0035 mol, 75%) as an oil. ^{1}H NMR (DMSO) d 8.75 (s, 1H), 8.5 (bs, 2H), 8.2-8.05 (m, 3H), 7.75-7.70 (m, 2H), 4.6 (s, 2H), 3.95 (m, 3H).

Part C - To a solution of methyl 8-aminomethyl-2-naphthoate (0.75 g, 0.0035 mol) in dry tetrahydrofuran (50 mL), cooled to 0°C, was added a solution of lithium hydroxide (0.5 M, 5.83 mL). All was stirred at ambient temperature over 20 hours. Another aliquot of lithium hydroxide was added and all was stirred for an additional 20 hours. The solid was collected and the filtrate was evaporated to dryness under reduced pressure. The solids were triturated with diethyl ether to give 8-aminomethyl-2-naphthoic acid (0.67 g, 0.0033 mol, 95%) as a white solid. mp = 223-225°C; ^{1}H NMR (DMSO) d 8.6 (s, 1H), 8.1-7.9 (m, 1H), 7.8-7.7 (m, 4H), 7.55-7.5 (m, 1H), 7,45-7.35 (m, 2H), 4.2 (s, 2H).

Part D - A solution of 8-aminomethyl-2-naphthoic acid (0.50 g, 0.00025 mol) and triethylamine (0.038 mL, 0.028 g, 0.000275 mol) in aqueous tetrahydrofuran (50%, 5 mL) was added, portionwise as a solid, 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (0.068 g, 0.000275 mol). All was stirred at ambient temperature over 5 hours. The solution was concentrated to half volume and extracted with diethylether. The aqueous layer was then acidified to a pH of 1.0 using hydrochloric acid (1N) and then extraced with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated to dryness under reduced pressure to give the title compound, N-(BOC)-8-aminomethyl-2-naphthoic acid (0.050 g, 0.00017 mol) as a white solid. mp = 190-191°C; ^{1}H NMR (DMSO) d 13.1 (bs, 1H), 8.8 (s, 1H), 8.0 (q, 2H, J=7.9 Hz), 7.9 (d, 1H, J=8.1 Hz), 7.6 (t, 1H, J=7.5 Hz), 7.65-7.55 (m, 2H), 4.6 (d, 2H, J=5.5 Hz), 1.4 (s, 9H).

Synthesis of Cyclic Peptides

t-Butyloxycarbonyl-3-aminomethylbenzoic acid (Boc-Mamb) is coupled to oxime resin by a modification of the method described by DeGrado and Kaiser (1980) *J. Org. Chem.* **45**, 1295 using 1 equivalent of the 3-aminomethylbenzoic acid (with respect to the substitution level of the resin), 1 equivalent of HBTU, and 3 equivalent of NMM. Alternatively, Boc-Mamb (1 equivalent) may be coupled to the oxime resin using 1 equivalent each of DCC and DMAP in methylene chloride. Coupling times range from 15 to 96 hours. The substitution level is then determined using either the picric acid test (Sarin, Kent, Tam, and Merrifield, (1981) *Anal. Biochem.* **117**, 145-157) or the quantitative ninhydrin assay (Gisin (1972) *Anal. Chim. Acta* **58**, 248-249). Unreacted oxime groups are blocked using 0.5 M trimethylacetylchloride / 0.5 M diisopropylethylamine in DMF for 2 hours. Deprotection of the Boc protecting group is accomplished using 25% TFA in DCM for 30 minutes. The remaining amino acids or amino acid derivatives are coupled using between a two and ten fold excess (based on the loading of the first amino acid or amino acid derivative) of the appropriate amino acid or amino acid derivatives and HBTU in approximately 8 ml of DMF. The resin is then neutralized in situ using 3 eq. of NMM (based on the amount of amino acid used) and the coupling times range from 1 hour to several days. The completeness of coupling is monitored by qualitative ninhydrin assay, or picric acid assay in cases where the amino acid was coupled to a secondary amine. Amino acids are recoupled if necessary based on these results.

After the linear peptide had been assembled, the N-terminal Boc group is removed by treatment with 25% TFA

in DCM for 30 minutes. The resin is then neutralized by treatment with 10% DIEA in DCM. Cyclization with concomitant cleavage of the peptide is accomplished using the method of Osapay and Taylor ((1990) *J. Am. Chem. Soc.*, **112**, 6046) by suspending the resin in approximately 10 ml/g of DMF, adding one equivalent of HOAc (based on the loading of the first amino acid), and stirring at 50-60°C for 60 to 72 hours. Following filtration through a scintered glass funnel, the DMF filtrate is evaporated, redissolved in HOAc or 1:1 acetonitrile: H_2O, and lyophilized to obtain protected, cyclized material. Alternatively, the material may be dissolved in methanol and precipitated with ether to obtain the protected, cyclized material. This is then treated using standard procedures with anhydrous hydrogen fluoride (Stewart and Young (1984) "Solid Phase Peptide Synthesis", 2nd. edition, Pierce Chemical Co., 85) containing 1 ml/g *m*-cresol or anisole as scavenger at 0°C for 20 to 60 minutes to remove side chain protecting groups. The crude product may be purified by reversed-phase HPLC using a 2.5 cm preparative Vydac C18 column with a linear acetonitrile gradient containing 0.1% TFA to produce pure cyclized material. The following N-α-Boc-protected amino acids may be used for the syntheses: Boc-Arg(Tos), Boc-N-a-MeArg(Tos), Boc-Gly, Boc-Asp(OcHex), Boc-3-aminomethyl-4-iodo-benzoic acid, Boc-D-Ile, Boc-NMeAsp(OcHex), Boc-NMe-Mamb, Boc-D-Phg, Boc-D-Asp(OBzl), Boc-L-Asp(OcHex), Boc-aMe-Asp(OcHex), Boc-bMe-Asp(OcHex), Boc-L-Ala, Boc-L-Pro, Boc-D-Nle, Boc-D-Leu, Boc-D-Val, Boc-D-2-aminobutyric acid (Boc-D-Abu), Boc-Phe, Boc-D-Ser(Bzl), Boc-D-Ala, Boc-3-aminomethylbenzoic acid (Boc-Mamb), Boc-D-Lys(2-ClZ), Boc-β-Ala, Boc-D-Pro, Boc-D-Phe, Boc-D-Tyr(Cl_2Bzl), Boc-NMe-Amf(CBZ), Boc-aminotetralin-carboxylic acid, Boc-aminomethylnaphthoic acid, Boc-4-aminomethylbenzoic acid, or Boc-NMeGly.

The synthesis of the compounds of the invention is further exemplified in PCT Patent Application International Publication Number WO93/07170 (Publication Date April 15, 1993) and as set forth below. The Tables below set forth representative compounds of the present invention.

Example 3a

cyclo-(Abu-NMeArg-Gly-Asp-Mamb); the compound of formula (II) wherein J = Abu, K = NMeArg, L = Gly, M = Asp, R^1 = H, R^2 = H

The title compound was prepared using the general procedure described for cyclo-(D-Val-NMeArg-Gly-Asp-Mamb) (Example 4). The DCC/DMAP method was used for attachment of Boc-Mamb to the oxime resin. TBTU was used as the coupling reagent. The peptide was prepared on a 0.596 mmol scale to give the protected cyclic peptide (182 mg,38.4%). The peptide (176 mg) and 0.176 mL of anisole were treated with anhydrous hydrogen fluoride at 0°C for 20 minutes. The crude material was precipitated with ether, redissolved in aqueous acetonitrile, and lyophilized to generate the title compound (116 mg; 90.4%; calculated as the fluoride salt). Purification was accomplished by reversed-phase HPLC on a preparative Vydac C18 column (2.5 cm) using a 0.45%/ min. gradient of 9 to 27% acetonitrile containing 0.1% TFA and then lyophilized to give the TFA salt of the title compound as a fluffy white solid (1.92% recovery, overall yield 0.574%); FAB-MS: [M+H] = 561.39.

Example 4

Crystallization of the Compound of Example 4 and the Preparation of Salt Forms of the Compound of Example 4

It has been discovered that the compounds of the present invention may be isolated by crystallization of the compound from organic and aqueous solvents.

The zwitterion of Example 4 was converted to the mesyl (methanesulfonate) salt of Example 4 (Example 4 (methane-sulfonate)) by refluxing the zwitterion with stirring in isopropanol at 25 mg/ml and slowly adding a solution of 1.0 molar equivalent methanesulfonic acid (correcting for the water content of the zwitterion) dissolved in isopropanol. The heat was turned off and the solution cooled to 5°C in an ice bath. After stirring 1 hour, the solution was filtered and the solid rinsed three times with cold isopropanol and dried under vacuum to constant weight.

The following salts of the compound of Example 4 were prepared using the same procedure, by adding 1.0 equivalent of the appropriate acid:

Example 4 (biphenylsulfonate):
zwitterion + 1.0 equivalent biphenylsulfonic acid.

Example 4 (α-naphthalenesulfonate):
zwitterion + 1.0 equiv. α-naphthalenesulfonic acid.

Example 4 (β-naphthalenesulfonate):
zwitterion + 1.0 equiv. β-naphthalenesulfonic acid.

Example 4 (benzenesulfonate):
zwitterion + 1.0 equiv. benezene-sulfonic acid.

Example 4 (*p*-toluenesulfonate):
zwitterion + 1.0 equiv. *p*-toluene-sulfonic acid.

The following salts of the compound of Example 4 were prepared by crystallization of the compound from aqueous systems.

Example 4 (sulfate):
10 mg amorphous Example 4 (made by lyophilizing the zwitterion from a solution of 2 molar equivalents of acetic acid in water) dissolved per ml 1 N H_2SO_4, pH adjusted to 2.5. On standing at room temperature, a precipitate formed. This was filtered through a sintered glass funnel and dried under vacuum to constant weight.

Example 4 (methanesulfonate (mesyl)):
100 mg amorphous DMP728 dissolved per ml water + 1.2 molar equiv. methanesulfonic acid (this was obtained as a 4M aqueous solution). On standing at room temperature, a large flat crystal was formed.

Example 4 (benzenesulfonate):
100 mg zwitterion dissolved per ml water + 1.2 equiv. benzenesulfonic acid added. On standing at room temeprature, a precipitate formed. This was filtered through a sintered glass funnel, rinsed with a small volume of isopropanol, and dried under vacuum to constant weight.

Example 4 (*p*-toluenesulfonate):
100 mg zwitterion dissolved per ml water + 1.2 molar equiv. toluenesulfonic acid added. On standing at room temperature, a precipitate formed. This was filtered through a sintered glass funnel and dried under vacuum to constant weight.

Example 17

cyclo-(D-Met-NMeArg-Gly-Asp-Mamb); the compound of formula (II) wherein J = D-Met, K = NMeArg, L = Gly, M = Asp, R^1 = H, R^2 = H

The title compound was prepared using the general procedure described for cyclo-(D-Val-NMeArg-Gly-Asp-Mamb) (Example 4). The DCC/DMAP method was used for the attachment of Boc-Mamb to the resin. The peptide was prepared on a 0.179 mmol scale to give the protected cyclic peptide (105 mg, 69.7%). The peptide (105 mg) and 0.105 mL of anisole were treated with anhydrous hydrogen fluoride at 0°C for 20 minutes. The crude material was precipitated with ether, redissolved in aqueous acetonitrile, and lyophilized to generate the title compound (72 mg; 92.3% yield; calculated as the fluoride salt). Purification was accomplished by reversed-phase HPLC on a preparative Vydac C18 column (2.5 cm) using a 0.23%/ min. gradient of 14.4 to 23.4% acetonitrile containing 0.1% TFA and then lyophilized to give the TFA salt of the title compound as a fluffy white solid (13.2% recovery, overall yield 7.4%); FAB-MS: [M+H] = 607.3.

Example 401

cyclo-(D-Abu-NMeArg-Gly-D-Asp-Mamb); compound of formula (II) wherein J = D-Abu, K = NMeArg, L = Gly, M = D-Asp, R^1 = H, R^2 = H

The title compound was prepared using the general procedure described for cyclo-(D-Val-NMeArg-Gly-Asp-Mamb) (example 4). The DCC/DMAP method was used for attachment of Boc-Mamb to the oxime resin. TBTU was used as the coupling reagent. The peptide was prepared on a 0.596 mmol scale to give the protected cyclic peptide (273 mg, 57.6%). The peptide (263 mg) and 0.263

mL of anisole were treated with anhydrous hydrogen fluoride at 0°C for 20 minutes. The crude material was precipitated with ether, redissolved in aqueous acetonitrile, and lyophilized to generate the title compound (218 mg; greater than quantitative yield; calculated as the fluoride salt). Purification was accomplished by reversed-phase HPLC on a preparative Vydac C18 column (2.5 cm) using a 0.23%/ min. gradient of 10.8 to 19.8% acetonitrile containing 0.1% TFA and then lyophilized to give the TFA salt of the title compound as a fluffy white solid (40.4% recovery, overall yield 21.9%); FAB-MS: [M+H] = 561.37.

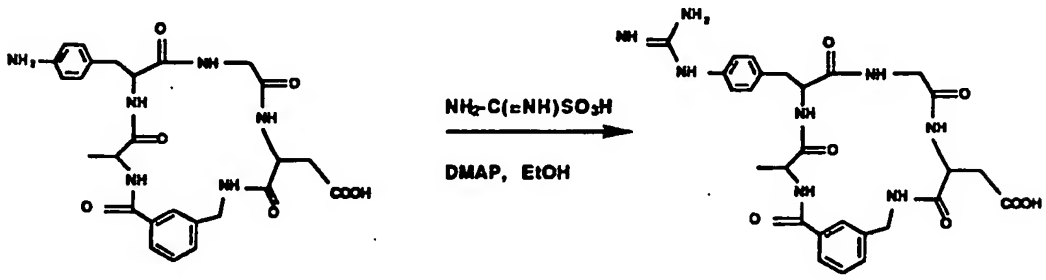
Example 402

cyclo-(D-Abu-D-NMeArg-Gly-Asp-Mamb); the compound of formula (II) J = D-Abu, K = D-NMeArg, L = Gly, M = Asp, R^1 = H, R^2 = H

The title compound was prepared using the general procedure described for cyclo-(D-Val-NMeArg-Gly-Asp-Mamb) (example 4). The DCC/DMAP method was used for attachment of Boc-Mamb to the oxime resin. TBTU was used as the coupling reagent. The peptide was prepared on a 0.596 mmol scale to give the protected cyclic peptide (241 mg, 50.8%). The peptide (235 mg) and 0.235 mL of anisole were treated with anhydrous hydrogen fluoride at 0°C for 20 minutes. The crude material was precipitated with ether, redissolved in aqueous acetonitrile, and lyophilized to generate the title compound (168 mg; 98.3%; calculated as the fluoride salt). Purification was accomplished by reversed-phase HPLC on a preparative Vydac C18 column (2.5 cm) using a 0.23%/ min. gradient of 12.6 to 21.6% acetonitrile containing 0.1% TFA and then lyophilized to give the TFA salt of the title compound as a fluffy white solid (2.3% recovery, overall yield 0.99%); FAB-MS: [M+H] = 561.36.

Example 403

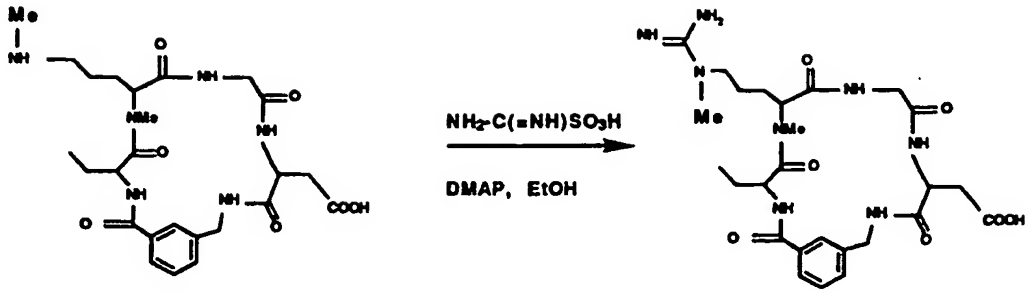
Cyclo-(D-Ala-*p*-guanidinyl-Phe-Gly-Asp-Mamb); the compound of formula (II) wherein J = D-Ala, K = p-guanidinyl-Phe, L = Gly, M = Asp R^1 = H, R^2 = H



Dissolved 25 mg (38.3 µmoles) of cyclo-(D-Ala-*p*-amino-Phe-Gly-Asp-Mamb) (TFA salt), 14.3 mg (114.9 umoles) formamidine sulfonic acid, and 18.7 mg (153.2 umoles) of 4-dimethyl-aminopyridine in 5 ml of ethanol in a 10 ml round bottom flask. Refluxed the mixture for 3 hours, then added an additional 14.3 mg of formamidine sulfonic acid and 18.7 mg of 4-dimethyl-aminopyridine. After refluxing for an additional 3 hours, the reaction was found to be ~75% complete by reversed-phase HPLC. The ethanol was evaporated under reduced pressure, and the residue was purified on a preparative Vydac C18 column (2.5 cm) using a 0.45%/min. gradient of 0 to 18% acetonitrile containing 0.1% TFA.
Lyophilization afforded the TFA salt of the title compound as a white solid (28% recovery), overall yield 26.4%); FAB-MS: [M+H] = 581.30.

Example 404

cyclo-(D-Abu-(DiNMe,guanidinyl-Orn)-Gly-Asp-Mamb); the compound of formula (II) wherein J = D-Abu, K = diNMe,guanidinyl-Orn , L = Gly, D = Asp, R^1 = H, R^2 = H



Dissolved 10.53 mg (16.3 μmoles) of cyclo-(D-Abu-diNMeOrn-Gly-Asp-Mamb) (TFA salt), 6.08 mg (48.99 umoles) formamidine sulfonic acid, and 8.00 mg (65.57 umoles) of 4-dimethyl-aminopyridine in 2.5 ml of ethanol in a 10 ml round bottom flask. Refluxed the mixture for 2 hours and then stirred at room temperature overnight. Refluxed for one hour, added an additional 6.08 mg of formamidine sulfonic acid and 8.00 mg of 4-dimethylaminopyridine and then refluxed for an additional 2 hours. Evaporated the ethanol under reduced pressure and purified the residue on a preparative Vydac C18 column (2.5 cm) using a 0.45%/min. gradient of 3.6 to 18% acetonitrile containing 0.1% TFA. Lyophilization afforded the TFA salt of the title compound as a white solid (57.2% recovery), overall yield 53.5%); FAB-MS: [M+H] = 575.34.

Examples 405

cyclo-(D-Abu-Di-NMeLys-Gly-Asp-Mamb); the compound of formula (II) wherein J = D-Abu, K = Di-NMeLys, L = Gly, M = Asp, R^1 = H, R^2 = H

cyclo-(D-Abu-NMeLys-Gly-Asp-Mamb); the compound of formula (II) wherein J = D-Abu, K = NMeLys, L = Gly, M = Asp, R^1 = H, R^2 = H

Di-N-methyl amino acid derivatives may be prepared using methods which have been described previously (Olsen, *J. Org. Chem.* (1970) 35: 1912) or, alternatively, through the use of NaH/CH_3I. The mono-NMe-Lysine amino acid was obtained as a side product during the synthesis of the corresponding di-NMe-lysine derivative. The title compounds were prepared using conventional solution phase peptide chemistry techniques described previously. Cyclo-(D-Abu-diNMeLys-Gly-Asp-Mamb) was obtained in 0.31% overall yield, FAB-MS: [M+H] = 547.3. Cyclo-(D-Abu-NMeLys-Gly-Asp-Mamb) was obtained in 0.25% overall yield, FAB-MS: [M+H] = 533.3.

Example 100a

cyclo-(D-Abu-NMeArg-Gly-Asp-3-aminomethyl-6-chlorobenzoic acid)

The title compound was prepare by the general solution-phase procedure described above for cyclo-(D-Val-NMeArg-Gly-Asp-Mamb), except that 4,4'-dinitrobenzophenone oxime was employed. The cyclic peptide (330 mg, 0.40 mmol) was deprotected with excess HF in the presence of anisole as scavenger. Purification was accomplished by reversed-phase HPLC on a preparative Vydac C18 column (2.5 cm) using a 1.0% / minute gradient of 10 to 38% acetonitrile containing 0.1% trifluoroacetic acid to give the TFA salt of the title compound (114 mg, 41%) as a fluffy white solid; ^1H NMR (D_6-DMSO) 9.00 (d, 1H), 8.40 (m, 2H), 7.50 (m, 1H), 7.40 (d, 1H), 7.30 (m, 2H), 7.15 (s, 1H), 7.00 (br s, 4H), 5.15 (dd, 1H), 4.65 (q, 1H), 4.50 (dd, 1H), 4.40 (q, 1H), 4.05 (dd, 1H), 3.95 (dd, 1H), 3.65 (dd, 1H), 3.10 (q, 2H), 3.05 (s, 3H), 2.75 (dd, 1H), 2.50 (m, 1H), 1.95 (m, 1H), 1.75 (m, 2H), 1.60 (m, 1H), 1.35 (m, 2H), 0.95 (t, 3H); FAB-MS: [M+H] = 595.4.

Example 100b

cyclo-(D-Abu-NMeArg-Gly-Asp-3-aminomethyl-6-iodobenzoic acid)

The title compound was prepare by the general solution-phase procedure described above for cyclo-(D-Val-NMeArg-Gly-Asp-Mamb), except that 4,4'-dinitrobenzophenone oxime was employed. The cyclic peptide (350 mg, 0.38 mmol) was deprotected with excess HF in the presence of anisole as scavenger. Purification was accomplished by reversed-phase HPLC on a preparative Vydac C18 column (2.5 cm) using a 1.0% / minute gradient of 10 to 38% acetonitrile containing 0.1% trifluoroacetic acid to give the TFA salt of the title compound (150 mg, 49%) as a fluffy white solid; ^{1}H NMR (D_6-DMSO) 8.90 (d, 1H), 8.40 (m, 2H), 7.70 (d, 1H), 7.50 (m, 1H), 7.30 (m, 1H), 7.05 (s, 1H), 7.00 (d, 1H), 7.00 (br s, 4H), 5.15 (dd, 1H), 4.65 (q, 1H), 4.45 (dd, 1H), 4.40 (q, 1H), 4.00 (q, 1H), 3.90 (q, 1H), 3.65 (dd, 1H), 3.10 (q, 2H), 3.05 (s, 3H), 2.70 (dd, 1H), 2.50 (m, 1H), 1.95 (m, 1H), 1.75 (m, 2H), 1.60 (m, 1H), 1.40 (m, 2H), 0.95 (t, 3H); FAB-MS: [M+H] = 687.3.

Example 100c

cyclo-(D-Abu-NMeArg-Gly-Asp-3-aminomethyl-6-methylbenzoic acid)

(the compound of formula (VII) wherein J = D-Abu, K = NMeArg, L = Gly, M = Asp, R^{10} = Me)

The title compound was prepare by the general solution-phase procedure described above for cyclo-(D-Val-NMeArg-Gly-Asp-Mamb), except that 4,4'-dinitrobenzophenone oxime was employed. The cyclic peptide (130 mg, 0.16 mmol) was deprotected with excess HF in the presence of anisole as scavenger. Purification was accomplished by reversed-phase HPLC on a preparative

Vydac C18 column (2.5 cm) using a 1.0% / minute gradient of 10 to 38% acetonitrile containing 0.1% trifluoroacetic acid to give the TFA salt of the title compound (31 mg, 28%) as a fluffy white solid; ^{1}H NMR (D_6-DMSO) 8.70 (d, 1H), 8.40 (d, 1H), 8.30 (t, 1H), 7.50 (m, 1H), 7.45 (m, 1H), 7.15 (q, 2H), 7.05 (s, 1H), 7.00 (br s, 4H), 5.15 (dd, 1H), 4.65 (q, 1H), 4.45 (m, 2H), 4.00 (m, 2H), 3.65 (dd, 1H), 3.10 (q, 2H), 3.05 (s, 3H), 2.75 (dd, 1H), 2.50 (m, 1H), 2.30 (s, 3H), 2.00 (m, 1H), 1.75 (m, 2H), 1.60 (m, 1H), 1.35 (m, 2H), 0.95 (t, 3H); FAB-MS: [M+H] = 575.4.

Representative Prodrugs

Step 1: N^{α}-benzyloxycarbonyl-N^{α}-methyl-4-cyano-L-2-aminobutyric acid

Z-Gln (28.03 g, 100 mmol) was dissolved in 300 mL THF in a flask bottle protectected from moisture and to it was added 100 mL 1.93 M phosgene in toluene (193 mmol). The solution was stirred at room temperature for 2 h and concentrated at 30^0 C to 200 mL. Water (200 mL) was added slowly with stirring. After stirring at room temperature for 2 h, the organic phase was seperated, and the water phase was extracted with ethyl acetate twice. The combined organic solution was washed with brine four times, dried ($MgSO_4$), and concentrated. The oily product was dried over KOH overnight.

The dried oily product was taken up in 300 mL dry THF and 49.8 mL (800 mmol) methyl iodide in a flask bottle protected from moisture and the solution was cooled in an ice bath. To it was slowly added 10 g sodium hydride (250 mmol, 60% dispersion in oil). The mixture was stirred in the ice bath for 1 h and then at room temperature for 22 h. Ethyl acetate (50 mL) was added, and after stirring for 10 min, 100 mL water was added slowly. The solution was acidified with a few

drops of 4 N HCl to pH8-9 and then concentrated at 30^0 C to remove the organic solvents. Water (100 mL) was added followed by 10 mL 0.1 N sodium thiosulfate, and the solution was extracted with ether twice. The water layer was cooled in an ice bath and to it was slowly added 4 N HCl to pH 3 with stirring. The product , which crystallized during the acidification, was filtered, washed with water several times, and dried. Yield 26.0 g (94%). mp 81-83^0 C. ^{1}H-NMR ($CDCl_3$): δ=2.15 (m, 1H); 2.38 (m, 1H); 2.42 (m, 2H); 2.96 & 2.98 (2 s, *cis & trans* N-CH_3); 4.62 (m, 1H); 4.90 (b, 1H); 5.19 (s, 2H); 7.35 (m, 5H).

Step 2: N^{α}-methyl-4-cyano-L-2-aminobutyric acid-N-carboxyanhydride

To a solution of example 1 (11.05 g, 40 mmol) in 50 mL dry THF cooled in an ice bath was added phosphorus pentachloride (15 g, 72 mmol) and the mixture was stirred for 2 h and concentrated to dryness. The residue was triturated with petroleum ether to give a solid which was filtered, washed with petroleum ether and dissolved in dry acetonitrile. Insoluble material was filtered off and the solution was concentrated. The solid was washed with cold ether and dried. Yield 5.86 g (87%). mp 90-92^0 C. ^{1}H-NMR ($CDCl_3$): δ=2.18 (m, 1H); 2.39 (m, 1H); 2.60 (m, 2H); 3.02 (s, 3H); 4.28 (m, 1H).

Step 3: N-Boc-D-2-aminobutyryl-N^{α}-methyl-4-cyano-L-2-aminobutyryl-glycine t-butyl ester

To a solution of glycine *t*-butyl ester hydrochloride (3.68 g, 22 mmol) in 40 mL chloroform and 4.84 mL N-methylmorpholine cooled to -40^0 C was added a solution of example 2 (3.36 g, 20 mmol) in 20 mL dry acetonitrile, the solution was stirred at -20^0 C for 1 h, and the solvent was reduced to about 10 mL.

To a solution of N-Boc-*D*-2-aminobutyric acid dicyclohexylamine salt (8.08 g, 21 mmol) in 30 mL chloroform cooled to -10^0 C was added diphenylphosphinic chloride (3.91 mL, 20.5 mmol) and the mixture was stirred at -5 to -10^0 C for 1 h. To it was added the above prepared solution (10 mL) followed by 2.42 mL N-methylmorpholine. The mixture was stirred at 0 to -5^0 C for 24 h, and then concentrated. Ethyl acetate was added and insoluble material was filtered off. The filtrate was washed with $NaHCO_3$ four times and with brine three times, dried over $MgSO_4$, and concentrated to a small amount at which time the product crystallized. Petroleum ether was added, and after cooling, the solid was filtered, washed with petroleum ether, and dried. Yield 6.2 g (70%). mp 90-92^0 C. FAB-MS (MH^+): Calculated 441.3; Found 441.3.

Step 4: N-Boc-D-2-aminobutyryl-N$^{\alpha}$-methyl-N$^{\omega}$, N$^{\omega'}$-(bisbenzyloxycarbonyl)-L-arginyl-glycine t-butyl ester

The compound of Step 3 (4.63 g, 10.5 mmol) was dissolved in 70 mL methanol in a Parr bottle and to it was added a cold solution of 1.2 mL concentrated hydrochloric acid (38%) in 10 mL methanol followed by 200 mg platinum(IV) oxide. The mixture was hydrogenated at 55 psi for 1 h, the catalyst was filtered off, and 2.09 mL (15 mmol) triethylamine was added. The solvent was removed under reduced pressure and the residue was taken up in 20 mL THF. To it was added N, N'-bisbenzyloxycarbonyl-S-methylisothiourea (3.58 g, 10 mmol) followed by 2.09 mL (15 mmol) triethylamine. The mixture was stirred overnight during which time the bottle was evacuated several times to remove the byproduct methanethiol. Ethyl acetate was added, and the solution was washed with 1% citric acid, brine, 5% $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Crystallization from ethyl ether-petroleum ether gave

7.2 g (95%) product. FAB-MS (MH^+): Calculated 755.4; Found 755.4.

Step 5: D-2-aminobutyryl-N^{α}-methyl-N^{ω}, $N^{\omega'}$-(bisbenzyloxycarbonyl)-L-arginyl-glycine TFA salt

A solution of the compound of Step 4 (9 g, 11.9 mmol) in 90 mL 50% TFA in methylene chloride was stirred at room temperature for 2 h and the solution was concentrated at 30^0 C. Cold ether was added, and after standing, the solid was filtered, washed with ether, and dried. Yield 8.4 g (99%). FAB-MS (MH^+): Calculated 599.3; Found 599.3.

Step 6: 3-(aminomethyl)benzoic acid hydrochloride

3-cyanobenzoic acid (5.88 g, 40 mmol) was suspended in 50 mL THF and the mixture was warmed up with stirring. After all solid went into solution, 50 mL isopropanol was added and the solution was allowed to cool to room temperature. To it was added 4.2 mL precooled concentrated HCl followed by 300 mg platinum(IV) oxide. The mixture was hydrogenated at 55 psi overnight. Ether (50 mL) was added, and the precipitate was filtered, washed with ether and dissolved in methanol. The catalyst was filtered off and the solvent was removed under reduced pressure to give 6.2 g (82%) product. ^{1}H-NMR (DMSO-d_6): δ=4.08 (d, 2H); 7.53 (t, 1H); 7.80 (d, 1H); 7.94 (d, 1H); 8.10 (s, 1H); 8.65 (s, 3H).

Step 7: Fmoc-*L*-aspartyl(t-butyl)-3-(aminomethyl)-benzoic acid

To a solution of FmocAsp(Bu^t)OPfp (17.33 g, 30 mmol) and the compound of Step 6 (6.19 g, 33 mmol) in 50 mL DMF cooled in an ice bath was added 11.5 mL (66 mmol) diisopropylethylamine, and after stirring at room temperature for 5 h, 200 mL 5% citric acid was added and

the solution was extracted with ethyl acetate twice. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a solid which was washed with ether-petroleum ether and dried. Yield 16.3 g (100%). ^1H-NMR (DMSO-d_6): δ=1.35 (s, 8H); 2.48 (dd, 1H); 2.70 (dd, 1H); 4.2-4.4 (m, 6H); 7.30 (t, 2H); 7.4-7.5 (m, 4H); 7.7-7.9 (m, 7H); 8.55 (t, 1H); 12.92 (s, 1H).

Step 8: Fmoc-*L*-aspartyl(*t*-butyl)-3-(aminomethyl)benzoyl-*D*-2-aminobutyryl-N^a-methyl-N^w, $N^{w'}$-(bisbenzyloxycarbonyl)-*L*-arginyl-glycine

A mixture containing the compound of Step 7 (10.89 g, 20 mmol), pentafluorophenol (4.05 g, 22 mmol) and DCC (4.13 g, 20 mmol) in 50 mL THF was stirred at room temperature overnight. Dicyclohexylurea was filtered off, rinsed with THF, and the filtrate was concentrated. To it was added a solution of the compound of Step 5 (14.25 g, 20 mmol) in 40 mL DMF followed by 7.32 mL (42 mmol) diisopropylethylamine. The mixture was stirred at room temperature for 4 h, insoluble material was filtered off, and the filtrate was added to 200 mL 3% citric acid with stirring. The solution was extracted with ethyl acetate twice and the combined extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was triturated with ether-petroleum ether to give 22 g (98%) product. FAB-MS (MH^+): Calculated 1125.5; Found 1125.7.

Step 9: Cyclo[*L*-aspartyl(*t*-butyl)-3-(aminomethyl)benzoyl-*D*-2-aminobutyryl-N^ω, $N^{\omega'}$-(bisbenzyloxycarbonyl)-*L*-arginyl-glycyl]

A solution of the compound of Step 8 (22.5 g, 20 mmol) and 4-dimethylaminopyridine (14.66 g, 120 mmol) in 100 mL DMF was stirred overnight at room temperature and added slowly to a solution of TBTU (6.42 g, 20 mmol) in 200 mL DMF over 3 h and stirring was continued for 1 h.

Ethyl acetate (1000 mL) was added and the solution was washed with 1% citric acid 2 times, brine 3 times and concentrated to dryness. The residue was taken up in THF and after filtration, the solvent was removed under reduced pressure to give a solid which was washed with ether and dried. Yield 16 g (90%). FAB-MS (MH^+): Calculated 885.4; Found 885.2.

Step 10: Cyclo[*L*-aspartyl-3-(aminomethyl)benzoyl-*D*-2-aminobutyryl-N^{ω}, $N^{\omega'}$-(bisbenzyloxycarbonyl)-*L*-arginyl-glycyl]

A solution of the compound of Step 9 (16 g, 18 mmol) in 200 mL 50% TFA in methylene chloride was stirred at room temperature for 1.5 h and then concentrated. The residue was triturated with ether to give 14.5 g (97%) product. FAB-MS (MH^+): Calculated 829.4; Found 829.1.

Example 301

Cyclo[*L*-aspartyl(acetoxymethyl)-3-(aminomethyl)benzoyl-*D*-2-aminobutyryl-*L*-arginyl-glycyl]

A mixture containing the compound of Step 10 (above) (1.42 g, 1.7 mmol), bromomethyl acetate (980 mL, 10 mmol) and triethylamine (976 mL, 7 mmol) in 10 mL DMF was stirred at room temperature overnight. Ethyl acetate was added and the solution was washed with brine 3 times, dried ($MgSO_4$), concentrated, and dried. The residue was taken up in 8 mL DMF and to it was added 130 mL (2 mmol) methanesulfonic acid followed by 150 mg 10% palladium on carbon. The mixture was hydrogenated at atmospheric pressure for 2 h, the catalyst was filtered off, and the solution was diluted with water. Purification using semipreparative HPLC gave 650 mg (51) pure product. FAB-MS (MH^+): Calculated 633.3; Found 633.2.

Example 308

Cyclo[*L*-aspartyl(pivaloyloxymethyl)-3-(aminomethyl)benzoyl-*D*-2-aminobutyryl-*L*-arginyl-glycyl]

A mixture containing the compound of Step 10 (above) (4.14 g, 5 mmol), chloromethyl pivalate (4.3 mL, 30 mmol), triethylamine (2.8 mL, 20 mmol), NaI (4.5 g, 30 mmol) in 10 mL DMF was stirred at room temperature for 18 h. Ethyl acetate (100 mL) was added and the solution was washed with brine 3 times, dried ($MgSO_4$), and concentrated. The residue was taken up in 15 mL ethyl acetate and passed through a silica gel column using ethyl acetate-THF (1:1) as eluent to give 1.5 g pure product. The product was dissolved in 10 mL DMF and hydrogenated at atmospheric pressure using 10% palladium on carbon (130 mg) in the presence of methanesulfonic acid (100 mL) for 2 h. The catalyst was filtered off, rinsed with DMF, and the solution was diluted with water. Purification using semipreparative HPLC gave 1 g (26%) pure product. FAB-MS (MH^+): Calculated 675.3; Found 675.3.

Example 351

Cyclo[*L*-aspartyl-(isopropyloxycarbonyl-oxymethyl)-3-aminomethyl)benzoyl-*D*-2-aminobutyryl-*L*-arginyl-glycyl]

A mixture containing the compound of Step 10 (4.14 g, 5 mmol), chloromethyl isopropyl carbonate (4.58 g, 30 mmol), triethylamine (2.8 mL, 20 mmol), NaI (4.5 g, 30 mmol) in 10 mL DMF at stirred at room temperature for 18 h. Ethyl acetate (100 mL) was added and the solution was washed with brine 3 times, dried ($MgSO_4$), and concentrated. The residue was taken up in 10 mL ethyl acetate-THF (1:1) and passed through a silica column using ethyl acetate-THF (1:1) as eluent to give 1.6 g

product. The product was dissolved in 10 mL DMF and hydrogenated at atmospheric pressure using 10% palladium on carbon (150 mg) in the presence of 130 mL for 2 h. The catalyst was filtered off, rinsed with DMF, and the solution was diluted with water. Purification using semipreparative HPLC gave 1g (25%) pure product. FAB-MS (MH^+): Calculated 667.3; Found 667.3.

Incorporated herein by reference in their entirety are the following copending, commonly assigned U.S. Patent Applications which are filed on the same day as the present application: Attorney Docket No. DM-6535, named inventors Maduskuie and Pesti; Attorney Docket No. DM-6650, named inventors Zhang, Ma, and De Grado; and Attorney Docket No. DM-6665, named inventors De Grado, Dorow, Ward, and Xue.

Utility

The compounds of this invention possess antiplatelet efficacy, as evidenced by their activity in standard platelet aggregation assays or platelet fibrinogen binding assays, as described below. A compound is considered to be active in these assays if it has an IC_{50} value of less than about 1 mM. Platelet aggregation and fibrinogen binding assays which may used to demonstrate the antiplatelet activity of the compounds of the invention are described below.

Platelet Aggregation Assay: Venous blood was obtained from the arm of a healthy human donor who was drug-free and aspirin-free for at least two weeks prior to blood collection. Blood was collected into 10 ml citrated Vacutainer tubes. The blood was centrifuged for 15 minutes at 150 x g at room temperature, and

platelet-rich plasma (PRP) was removed. The remaining blood was centrifuged for 15 minutes at 1500 x g at room temperature, and platelet-poor plasma (PPP) was removed. Samples were assayed on a aggregometer (PAP-4 Platelet Aggregation Profiler), using PPP as the blank (100% transmittance). 200 µl of PRP was added to each micro test tube, and transmittance was set to 0%. 20 µl of various agonists (ADP, collagen, arachidonate, epinephrine, thrombin) were added to each tube, and the aggregation profiles were plotted (% transmittance versus time). The results were expressed as % inhibition of agonist-induced platelet aggregation. For the IC_{50} evaluation, the test compounds were added at various concentrations prior to the activation of the platelets.

Platelet-Fibrinogen Binding Assay: Binding of ^{125}I-fibrinogen to platelets was performed as described by Bennett et al. (1983) Proc. Natl. Acad. Sci. USA 80: 2417-2422, with some modifications as described below. Human PRP (h-PRP) was applied to a Sepharose column for the purification of platelet fractions. Aliquots of platelets (5 X 10^8 cells) along with 1 mM calcium chloride were added to removable 96 well plates prior to the activation of the human gel purified platelets (h-GPP). Activation of the human gel purified platelets was achieved using ADP, collagen, arachidonate, epinephrine, and/or thrombin in the presence of the ligand, ^{125}I-fibrinogen. The ^{125}I-fibrinogen bound to the activated, platelets was separated from the free form by centrifugation and then counted on a gamma counter. For an IC_{50} evaluation, the test compounds were added at various concentrations prior to the activation of the platelets.

The novel cyclic glycoprotein IIb/IIIa compounds of the invention also possess thrombolytic efficacy, that is, they are capable of lysing (breaking up) already formed platelet-rich fibrin blood clots, and thus are useful in treating a thrombus formation, as evidenced by their activity in the tests described below. Preferred cyclic compounds of the present invention for use in thrombolysis include those compounds having an IC_{50} value (that is, the molar concentration of the cyclic compound capable of achieving 50% clot lysis) of less than about 1 mM, more preferably an IC_{50} value of less than about 0.1 mM, even more preferably an IC_{50} value of less than about 0.01 mM, still more preferably an IC_{50} value of less than about 0.001 mM, and most preferably an IC_{50} value of about 0.0005 mM.

IC_{50} determinations may be made using a standard thrombolysis assay, as described below. Another class of preferred thrombolytic compounds of the invention include those compounds which have a Kd of < 100 nM, preferably < 10 nM, most preferably 0.1 to 1.0 nM.

Thrombolytic Assay: Venous blood was obtained from the arm of a healthy human donor who was drug-free and aspirin free for at least two weeks prior to blood collection, and placed into 10 ml citrated Vacutainer tubes. The blood was centrifuged for 15 minutes at 1500 x g at room temperature, and platelet rich plasma (PRP) was removed. To the PRP was then added 1 x 10^{-3} M of the agonist ADP, epinephrine, collagen, arachidonate, serotonin or thrombin, or a mixture thereof, and the PRP incubated for 30 minutes. The PRP was centrifuged for 12 minutes at 2500 x g at room temperature. The supernatant was then poured off, and the platelets remaining in the test tube were resuspended in platelet poor plasma (PPP), which served as a plasminogen source.

The suspension was then assayed on a Coulter Counter (Coulter Electronics, Inc., Hialeah, FL), to determine the platelet count at the zero time point. After obtaining the zero time point, test compounds were added at various concentrations. Test samples were taken at various time points and the platelets were counted using the Coulter Counter. To determine the percent of lysis, the platelet count at a time point subsequent to the addition of the test compound was subtracted from the platelet count at the zero time point, and the resulting number divided by the platelet count at the zero time point. Multiplying this result by 100 yielded the percentage of clot lysis achieved by the test compound. For the IC_{50} evaluation, the test compounds were added at various concentrations, and the percentage of lysis caused by the test compounds was calculated.

Platelet Granular Secretion Studies. The role of the claimed platelet GPIIb/IIIa receptor antagonists on the modulation of platelet granular secretion from the α-granules, dense granules or intracellular Ca^{+2} binding proteins was examined. This class of compounds did not have any significant effect on platelet granular secretion of plasminogen activator inhibitor type-1 (PAI-1) from α-granules, the mobilization of intracellular calcium stores or the secretion of the vasoconstrictor serotonin from the dense granules. However, other antiplatelet agents such as aspirin or the antithrombin hirudin has been shown to inhibit platelet granular secretion of the antifibrinolytic (PAI-1) or the vasoconstrictor (serotonin) . Hence the combination between a universal antiaggregatory as well as an inhibitor of platelet secretion might provide optimal clinical benefits.

The novel cyclic compounds of the invention are also useful in combination products, that is, in pharmaceutical compositions containing the novel cyclic compounds of the invention in combination with anti-coagulant agents such as warfarin or heparin, or antiplatelet agents such as aspirin, piroxicam or ticlopidine, or thrombin inhibitors such as boropeptides, hirudin or argatroban, or thrombolytic agents such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof. Such combination products possess anti-platelet and thrombolytic efficacy, as evidenced by their activity in the tests described below.

These and other uses for the novel cyclic compounds of this invention, and combination products containing the same, will be readily apparent from the disclosures herein.

Platelet GPIIb/IIIa Binding Affinity

In the human gel-purified platelet (h-GPP) ^{125}I-fibrinogen binding assay, representative compounds of the present invention demonstrated high affinity in inhibiting the ^{125}I-fibrinogen binding to h-GPP (IC_{50} = 5- 100 nM) regardless of the agonist used. In an enzyme-linked immunosorbent assay (ELISA) using purified GPIIb/IIIa receptors obtained from human platelets, the representative compounds of the invention demonstrated direct inhibition of fibrinogen binding to RGD recognition site(s), with an IC_{50} of 0.5-10 nM. The inhibitory efficacy of the presently claimed compounds on fibrinogen binding to the platelet GPIIb/IIIa receptor was shown to be related to the number of binding sites, as is evident from the decrease in IC_{50} when platelet number was decreased.

Compound A (Example 3) was shown to displace ^{125}I-fibrinogen bound to activated platelets . In this study, fibrinogen bound to activated platelets was incubated for 20 minutes prior to the addition of Compound A. This suggests a high affinity for Compound A in displacing fibrinogen from an already formed platelet-rich clot. This effect may explain the lytic efficacy of the compounds of the present invention. A high affinity binding (Kd = 0.1 nM) of ^{3}H-labeled Compound A to activated human platelets was determined based on Scatchard analysis. Additionally, in the purified GPIIb/IIIa-biotinylated fibrinogen ELISA, Compound A demonstrated competitive inhibitory efficacy with a K_i of 0.4 nM based on Michaelis-Menten analysis.

As shown below, in the human PRP aggregation assay, Compound A was shown not only to inhibit platelet aggregation induced by agonists, but also to deaggregate platelets after the initiation of aggregation. The deaggregation efficacy of Compound A was dependent on its concentration and the time of addition post-initiation of platelet activation. The earlier the addition of Compound A after the induction of aggregation, the greater its deaggregatory efficacy (Fig. Ia).

The effect of Compound A on the lysis of a pre-formed platelet-rich clot was also examined. In this regard, the thrombolytic efficacy of Compound A was also evaluated (Fig. Ib and II). Compounds A and B (Example 4) both demonstrated a significant lytic efficacy of pre-formed platelet rich-clot (Fig. Ib). Furthermore, Compound A demonstrated *in vitro* and *in vivo* synergistic efficacy with standard thrombolytics in lysing a platelet-rich thrombus (Fig. IIIb). A concentration-dependent lytic effect with an IC_{50} of 0.5-1.0 uM for compounds A and B was shown (Fig. Ib).

In contrast the tetrapeptide, RGDS, was shown to be ineffective under similar conditions (Fig. Ib).

Additionally, *in vitro* studies revealed synergy between Compound A (0.1-1.0 uM) and streptokinase, urokinase or t-PA in lysing a pre-formed platelet-rich clot (Fig. III). These results suggest an *in vivo* lytic potential for disclosed compounds of the present invention. Additionally, administration of these novel antagonists is expected to significantly reduce the dosage of a thrombolytic agent being used for clot lysis and the prevention of reocclusion and/or restenosis. In this regard, increasing evidence suggests that platelet activation after thrombolytic therapy might have a significant role in delaying reperfusion and abrupt closure. Hence, the disclosed analogs might be an effective adjunct to thrombolytic therapy or angioplasty.

The cyclic glycoprotein IIb/III antagonist compounds of this invention have also been shown to displace ^{125}I-fibrinogen bound to activated platelets in a platelet-fibrinogen binding assay similar to the platelet-fibrinogen binding assay previously described. The results indicated that the compounds have a high affinity in displacing fibrinogen from an already formed platelet-rich clot. Although not intending to be bound by any theory of operation, this result may help explain the surprising thrombolytic efficacy possessed by compounds of the invention, as illustrated in the preceding examples.

Figure 1

Representative cyclic compounds of the present invention, namely the compound of Example 3 (cyclo-(D-Abu-NMeArg-Gly-Asp-Mamb; the compound of formula (II)

wherein R^1 and R^2 are H, J is D-2-aminobutyric acid, K is α-N-methylarginine, L is glycine, and M is aspartic acid) (designated here as Compound A) and the compound of Example 4 (cyclo-(D-Val-NMeArg-Gly-Asp-Mamb; the compound of formula (II) wherein R^1 and R^2 are H, J is D-valine, K is α-N-methyl-arginine, L is glycine, and M is aspartic acid) (designated here as Compound B) were then tested in the human PRP aggregation assay (Figure Ia). Figure 1 shows the effect of 0.1 uM Compound on the reversal of the aggregatory response (deaggregation) to 10 uM ADP when added at 1.5 min post-initiation of aggregation.

In the human PRP aggregation assay, representative compounds of the present invention are shown not only to inhibit platelet aggregation induced by agonists, but also to deaggregate platelets after the initiation of aggregation (Figure Ia). The deaggregation efficacy of compound A was dependent on its concentration and the time of addition post-initiation of platelet activation. The earlier the addition of Compound A after the induction of aggregation, the greater its deaggregatory efficacy.

Compounds A and B were also tested at varying concentrations using the thrombolytic assay described above (Figure Ib). Figure Ib shows the lytic effect of Compound A and B on an already formed platelet rich clot. The clot was formed by incubating platelets with a mixture of agonists (TEAC mixture), which consists of thrombin (0.01 U/ml), epinephrine (250 uM), ADP (250 uM), and collagen (10 ug.ml), for 30 minutes. As a comparison, a linear peptide of sequence arginine-glycine-aspartic acid-serine (RGDS) was also tested in the thrombolytic assay. The results are shown in Figure I. The compounds of the invention (Compounds A and B) demonstrated a significant effect on the lysis of an already formed platelet-rich clot. As the results

indicated, Compounds A and B had IC_{50} values of about 0.5-1.0 uM. By comparison, the RGDS linear peptide was much less effective, even at substantially higher concentrations (IC_{50} > 1 mM).

Figure II

Compounds A and B was tested at a concentration of 0.001 mM using the thrombolytic assay described above, with platelet stimulation being carried out using 1 x 10^{-3} M concentration of ADP. As a comparison, the standard thrombolytics tissue plasminogen activator (tPA; 10 µg/ml), urokinase (UK; 900 units/ml) and streptokinase (SK; 500 units/ml) were also tested in the thrombolytic assay. The results are shown in Figure II. The compounds of the invention (Compounds A and B) demonstrated a significant effect on the lysis of an already formed platelet-rich clot, with Compound A providing significantly better clot lysis than tissue plasminogen activator, urokinase, and streptokinase, and Compound B providing significantly better clot lysis than streptokinase. As the results indicated, Compound A had an excellent lysis percentage of 70% or greater.

Figure III

Figure III shows the effect of 1 uM of Compound A on the lysis of an already formed platelet-rich clot. The clot was formed by the addition of TEAC mixture (which consists of thrombin (0.01 U/ml), epinephrine (250 uM), ADP (250 uM), and collagen (10 ug.ml)) for 30 minutes. Compound A resulted in significant clot lysis by itself as compared to tissue plasminogen activator (tPA; 10 µg/ml), urokinase (UK; 900 units/ml) and streptokinase (SK; 500 units/ml). A synergy (greater than additive effect between the standard thrombolytics

and the IIb/IIIa antagonist Compound A was demonstrated. Data represent mean ± SEM, n = 3 in each group.

Figure V

Compound C was tested at a concentration of 1 uM using the thrombolytic assay described above, both alone and in combination with the standard thrombolytics tissue plasminogen activator (tPA; 10 µg/ml), urokinase (UK; 900 units/ml) and streptokinase (SK; 500 units/ml). As the results indicate, the combination of Compound C with tissue plasminogen activator, urokinase or streptokinase gave a greater than additive effect than either agent alone.

Figure VI

Compound D was tested at a concentration of 1 uM using the thrombolytic assay described above, both alone and in combination with the standard thrombolytics tissue plasminogen activator (tPA; 10 µg/ml), urokinase (UK; 900 units/ml) and streptokinase (SK; 500 units/ml). As the results indicate, the combination of Compound D with tissue plasminogen activator, urokinase or streptokinase gave a greater than additive effect than either agent alone.

Figure VII

VII a.

Effect of 1 uM Compound A on the lysis of an already formed platelet-rich clot. The clot was formed by the addtion of TEAC mixture (which consists of thrombin [0.001 U/ml], epinephrine [250 uM], adenosine diphosphate [250 uM] and collagen [10 ug/ml] for 30 min. Compound A resulted in a significant clot lysis by itself as compared to SK (500 U/ml), UK (900 U/ml) or t-PA (10 ug/ml). A synergistic effect between the

standard thrombolytics and the IIb/IIIa antagonist Compound A was demonstrated. Data represent mean ± SEM, N=3 in each group.

VII b.

In vivo thrombolytic efficacy of Compound A and its interaction with standard thrombolytics: Compound A at 1 mg/kg I.V. in the modified Lucchesi model resulted in significant lysis of an already formed thrombus in the femoral artery. Additionally, Compound A in combination with sub-optimum doses of the standard thrombolytic, streptokinase (75 KU) resulted in a significant synergistic effect in fully lysing the thrombus with subsequent restoration of flow, and the prevention of reocclusion. Data represent mean ± SEM. n=3-6 in each group.

Figure VIII

Effects of Compound A vs saline, when given to anesthetized canine (male or female mongrel dogs) at 1.0 mg/kg I.V., on the incidence of femoral artery reocclusion post-thrombolysis with streptokinase (250-300 x 1000 IU/kg) or t-PA. Compound A resulted in 100% prevention of reocclusion for a period > 240 minutes, in comparison to saline-treated animals which were shown to reocclude at 42 ± 10 min. Compound A (1.0 mg/kg, I.V.) resulted in % prevention of the incidence of reocclusion post-thrombolysis with SK or t-PA. Data represents mean ± SEM, n=6 in each group.

Antiplatelet combination of the cyclic GPIIb/IIIa receptor antagonist of the present invention and aspirin and/or heparin.

Methods: Twelve purpose bred mongrel dogs (8-15 months of age) of either sex weighing between 8-12 kg were

anesthetized with thiamylal sodium (15 mg/kg, i.v.) and alpha-chloralose (100 ng/kg, i.v.) Dogs were placed on positive pressure ventilation (15 mg/kg (a) 20 breaths/min). The femoral artery and vein were dissected and cannulated for arterial blood pressure and heart rate monitoring, blood sampling, and intravenous injections.

Treatment Groups:

Group I (Saline): I.V. bolus of saline.

Group II (Aspirin): 10 mg/kg, po - 30 min prior to blood sampling.

Group III (Compound A): 0.08 mg/kg, I.V. bolus.

Group IV (Aspirin/Compound A): Aspirin at 10 mg/kg, po - 30 min prior to the administration of Compound A at 0.08 mg/kg, i.v.

(a) Serial blood samples were withdrawn for ex vivo platelet agregation and platelet counts.

(b) Bleeding time (min) was monitored over time as well.

(c) Plasma levels of Compound A were determined by an ELISA in all groups.

Results: The Compound A/aspirin, Compound A/heparin, and Compound A/warfarin combinations demonstrated an improved antiplatelet efficacy as compared to Compound A alone. This was achieved without any significant effects on bleeding time or platelet counts.

Dosage and Formulation

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action, glycoprotein IIb/IIIa (GPIIb/IIIa), in the body of a mammal. They can be

administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents, such as a second antiplatelet agent such as aspirin, piroxicam, or ticlopidine which are agonist-specific, or an anti-coagulant such as warfarin or heparin, or a thrombin inhibitor such as a boropeptide, hirudin or argatroban, or a thrombolytic agent such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof. The compounds of the invention, or compounds of the invention in combination with other therapeutic agents, can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage of the novel cyclic compounds of this invention administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. A daily dosage of active ingredient can be expected to be about 0.01 to 10 milligrams per kilogram of body weight.

Dosage forms (compositions suitable for administration) contain from about 1 milligram to about 100 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs,

syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

The combination products of this invention, such as the novel cyclic IIb/IIIa antagonist compounds of this invention in combination with an anti-coagulant agent such as warfarin or heparin, or an anti-platelet agent such as aspirin, piroxicam or ticlopidine, or a thrombin inhibitor such as a boropeptide, hirudin or argatroban, or a thrombolytic agent such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof, can be in any dosage form, such as

those described above, and can also be administered in various ways, as described above.

In a preferred embodiment, the combination products of the invention are formulated together, in a single dosage form (that is, combined together in one capsule, tablet, powder, or liquid, etc.). When the combination products are not formulated together in a single dosage form, the cyclic glycoprotein IIb/IIIa compounds of this invention and the anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent may be administered at the same time (that is, together), or in any order, for example the compounds of this invention are administered first, followed by administration of the anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent. When not administered at the same time, preferably the administration of the compound of this invention and any anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent occurs less than about one hour apart, more preferably less than about 30 minutes apart, even more preferably less than about 15 minutes apart, and most preferably less than about 5 minutes apart. Preferably, administration of the combination products of the invention is oral. The terms oral agent, oral inhibitor, oral compound, or the like, as used herein, denote compounds which may be orally administered. Although it is preferable that the cyclic IIb/IIIa antagonist compounds of this invention and the anti-coagulant agent, anti-platelet agent, thrombin inhibitor, and/or thrombolytic agent are both administered in the same fashion (that is, for example, both orally), if desired, they may each be administered in different fashions (that is, for example, one component of the combination product may be administered orally, and another component may be administered

intravenously). The dosage of the combination products of the invention may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

Although the proper dosage of the combination products of this invention will be readily ascertainable by one skilled in the art, once armed with the present disclosure, by way of general guidance, where the cyclic compounds of this invention are combined with anti-coagulant agents, for example, typically a daily dosage may be about 0.01 to 10 milligrams of the cyclic compound of this invention and about 1 to 7.5 milligrams of the anticoagulants, preferably about 0.1 to 1 milligrams of the cyclic compounds of this invention and about 1 to 5 milligrams of the anti-coagulants, per kilogram of patient body weight. With regard to a typical dosage form of this type of combination product, such as a tablet, the novel compounds of this invention generally may be present in an amount of about 5 to 10 milligrams, and the anti-coagulants in an amount of about 1 to 5 milligrams.

Where the novel compounds of this invention are combined with another anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the cyclic compounds of this invention and about 50 to 150 milligrams of the additional anti-platelet agents, preferably about 0.1 to 1 milligrams of the novel compounds of this invention and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight. With regard to a typical dosage form of this type of combination product, such as a tablet, the novel compounds of this invention

may be present, for example, in an amount of about 5 milligrams, and the additional anti-platelet agent in an amount of about 150 milligrams, or, for example, in an amount of about 25 milligrams of the cyclic compound of this invention and about 50 milligrams of the additional antiplatelet agent.

Further, in terms of general guidance, where the novel compounds of this invention are combined with thrombolytic agents, typically a daily dosage may be about 0.1 to 1 milligrams of the cyclic compound of this invention, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolyic agent when administered alone may be reduced by about 70-80% when administered with a compound of the present invention. With regard to a typical dosage form of this type of combination product, such as a tablet, the novel compounds of this invention may be present, for example, in an amount of about 10 milligrams.

As discussed above, where two or more of the foregoing therapeutic agents are combined or co-administered with the compounds of this invention, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the usual dosage of the agent when administered alone, in view of the additive or synergistic effect which would be obtained as a result of addition of further agents in accordance with the present invention.

Particularly when provided as a single dosage form, the potential exists for a chemical interaction between the combined active ingredients (for example, a novel compound of this invention and an anti-coagulant such as warfarin or heparin, or a novel compound of this invention and an anti-platelet agent such as aspirin,

piroxicam or ticlopidine, or a novel compound of this invention and a thrombin inhibitor such as a boropeptide, hirudin or argatroban, or a novel compound of this invention and a thrombolytic agent such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof). For this reason, the preferred dosage forms of the combination products of this invention are formulated such that although the active ingredients are combined in a single dosage form, the physical contact between the active ingredients is minimized (that is, reduced).

In order to minimize contact, one embodiment of this invention where the product is orally administered provides for a combination product wherein one active ingredient is enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. Another embodiment of this invention where oral administration is desired provides for a combination product wherein one of the active ingredients is coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of

hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

Dosage forms of the combination products of the present invention wherein one active ingredient is enteric coated can be in the form of tablets such that the enteric coated component and the other active ingredient are blended together and then compressed into a tablet or such that the enteric coated component is compressed into one tablet layer and the other active ingredient is compressed into an additional layer. Optionally, in order to further separate the two layers, one or more placebo layers may be present such that the placebo layer is between the layers of active ingredients. In addition, dosage forms of the present invention can be in the form of capsules wherein one active ingredient is compressed into a tablet or in the form of a plurality of microtablets, particles, granules or non-perils, which are then enteric coated. These enteric coated microtablets, particles, granules or non-perils are then placed into a capsule or compressed into a capsule along with a granulation of the other active ingredient.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

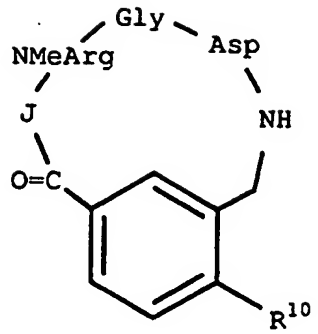
Pharmaceutical kits useful in, for example, the inhibition of platelet aggregation, the treatment of blood clots, and/or the treatment of thromboembolic

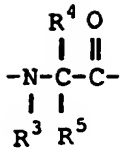
disorders, which comprise a therapeutically effective amount of a novel cyclic platelet glycoprotein IIb/IIIa compound of this invention along with a therapeutically effective amount of an anti-coagulant agent such as warfarin or heparin, or an antiplatelet agent such as aspirin, piroxicam or ticlopidine, or a thrombin inhibitor such as a boropeptide, hirudin or argatroban, or a thrombolytic agent such as tissue plasminogen activator, anistreplase, urokinase or streptokinase, or combinations thereof, in one or more sterile containers, are also within the ambit of the present invention. Sterilization of the container may be carried out using conventional sterilization methodology well known to those skilled in the art. The sterile containers of materials may comprise separate containers, or one or more multi-part containers, as exemplified by the UNIVIAL™ twopart container (available from Abbott Labs, Chicago, Illinois), as desired. The novel compounds of the invention and the anti-coagulant agent, anti-platelet agent, thrombin inhibitor, thrombolytic agent, and/or combinations thereof, may be separate, or combined into a single dosage form as described above. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as for example, one or more pharmaceutically acceptable carriers, additional vials for mixing the components, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, may also be included in the kit.

The Tables below set forth representative compounds of the present invention. In the Tables below the biological activity of the compounds is indicated as the

IC_{50} value in the platelet aggregation assay described above. The IC_{50} values are expressed as: +++ = IC_{50} value of less than 1 uM; ++ = IC_{50} value of 1 uM to 10 uM; and ; + = IC_{50} value of greater than 10 uM to about 100 uM. As used herein "uM" means micromolar. Where a mixture of isomers of a compound were tested, for example isomers designated as isomer 1 and isomer 2, the biological activity of the mixture is indicated in parentheses for each isomer.

Table 1



J= 

The optical isomer of J is indicated. R^{10}=H unless otherwise indicated.

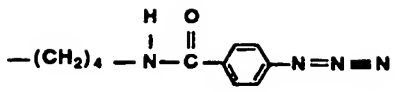
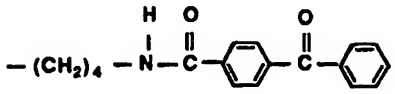
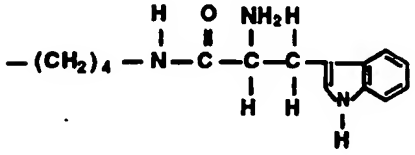
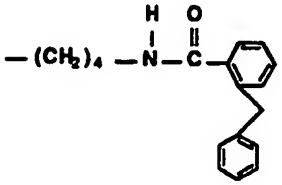
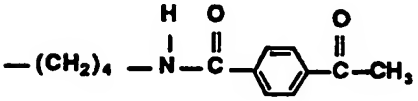
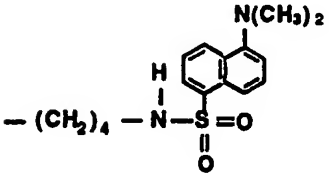
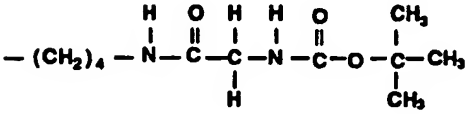
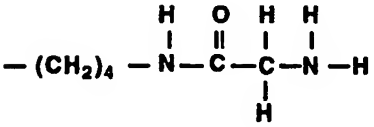
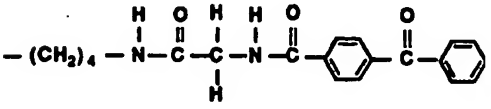
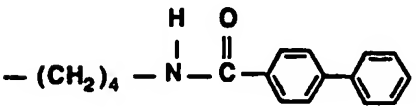
Ex. No.	R^3	R^4	R^5	FAB-MS (M+H)	Optical Isomer	IC_{50}
1	H	H	H	533.26		+++
2	H	H	CH_3	547.23	(D)	+++
2a	H	H	CH_3		(L)	
3	H	H	CH_2CH_3	561.46	(D)	+++
3a	H	H	CH_2CH_3		(L)	
3c	H	H	CH_2CH_3 R^{10}=I	687.33	(D)	+++
4	H	H	$CH(CH_3)_2$	575.45	(D)	+++
4a	H	H	$CH(CH_3)_2$		(L)	
5	H	H	$CH_2CH(CH_3)_2$	589.48	(D)	+++
5a	H	H	$CH_2CH(CH_3)_2$		(L)	
6	H	H	$CH_2CH_2CH_3$		(D)	
6a	H	H	$CH_2CH_2CH_3$		(L)	
7	H	H	$CH_2CH_2CH_2CH_3$	589.26	(D)	+++
7a	H	H	$CH_2CH_2CH_2CH_3$		(L)	
8	H	H	$(CH_2)_5CH_3$		(D)	
8a	H	H	$(CH_2)_5CH_3$		(L)	

Table 1 (continued)

Ex. No.	R^3	R^4	R^5	FAB-MS (M+H)	Optical Isomer	IC_{50}
9	H	H	$(CH_2)_7CH_3$		(D)	
9a	H	H	$(CH_2)_7CH_3$		(L)	
10	H	H	$C(CH_3)_3$		(D)	
10a	H	H	$C(CH_3)_3$		(L)	
11	H	H	phenyl	609.27	(D)	+++
11a	H	H	phenyl		(L)	
12	H	H	phenylmethyl	623.28	(D)	+++
12a	H	H	phenylmethyl		(L)	
13	H	H	CH_2OH		(D)	
13a	H	H	CH_2OH		(L)	
13b	H	H	$(CH_2)_3NH_2$		(D)	
13c	H	H	$(CH_2)_3NH_2$		(L)	
13d	H	H	$(CH_2)_3NHC(=NH)NH_2$		(D)	
13e	H	H	$(CH_2)_3NHC(=NH)NH_2$		(L)	
13f	H	H	$(CH_2)_4NH_2$	604.32	(D)	+++
13g	H	H	$(CH_2)_4NH_2$		(L)	
13h	H	H	$(CH_2)_4NHC(=NH)NH_2$		(D)	
13i	H	H	$(CH_2)_4NHC(=NH)NH_2$		(L)	
13j	H	H	$(CH_2)_5NH_2$		(D)	
13k	H	H	$(CH_2)_5NH_2$		(L)	
13l	H	H	$(CH_2)_5NHC(=NH)NH_2$		(D)	
13m	H	H	$(CH_2)_5NHC(=NH)NH_2$		(L)	
13n	H	H	$(CH_2)_4CH_3$		(D)	
13o	H	H	$(CH_2)_4CH_3$		(L)	

Table 1 (continued)

Ex. No.	R^3	R^4	R^5	FAB-MS (M+H)	Optical Isomer	IC_{50}
13p	H	H	$(CH_2)_6CH_3$		(D)	
13q	H	H	$(CH_2)_6CH_3$		(L)	
13r	H	H	$CH(CH_3)CH_2CH_3$	589.34	(D)	+++
13s	H	H	$CH(CH_3)CH_2CH_3$		(L)	
14	H	H	CH_2SH		(D)	
14a	H	H	CH_2SH		(L)	
15	H	H	CH_2OCH_3		(D)	
15a	H	H	CH_2OCH_3		(L)	
16	H	H	CH_2SCH_3		(D)	
16a	H	H	CH_2SCH_3		(L)	+++
17	H	H	$CH_2CH_2SCH_3$		(D)	
17a	H	H	$CH_2CH_2SCH_3$		(L)	
18	CH_3	H	H	547.34		+++
19	H	CH_3	CH_3			
20	H	CH_2CH_3	CH_2CH_3			
21	H	H	cyclopentyl		(D)	
21a	H	H	cyclopentyl		(L)	
22	H	H	cyclohexyl		(D)	
22a	H	H	cyclohexyl		(L)	+++
23	H	H	cyclohexylmethyl		(D)	
23c	H	H	cyclohexylmethyl		(L)	
23a	H	H	$CH(CH_3)_2$ R^{10}=I	701.37	(D)	
23b	H	H	$CH(CH_3)_2$ R^{10}=I		(L)	

23d	H	H		+++
23e	H	H		+++
23f	H	H		+++
23g	H	H		+++
23h	H	H		+++
23j	H	H		+++
23k	H	H		++
23l	H	H		+++
23m	H	H		+++
23n	H	H		+++

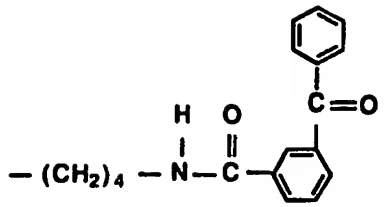
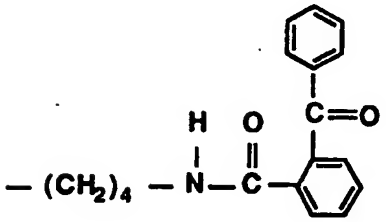
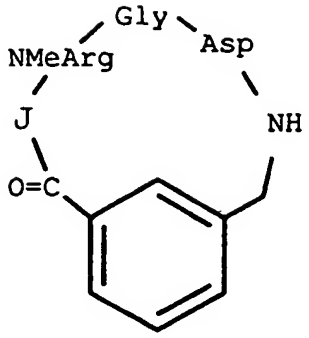
23o	H	H		+++
23p	H	H		++

Table 1 (continued)



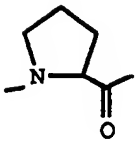
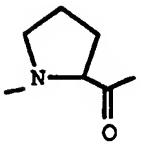
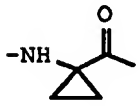
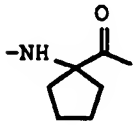
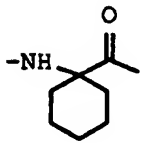
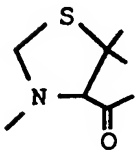
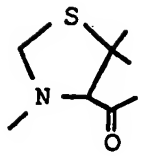
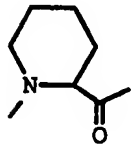
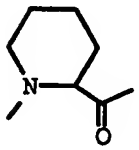
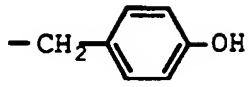
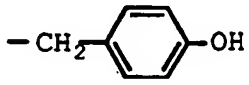
Ex. No.	J	FAB-MS (M+S)	Optical Isomer	IC_{50}
24		573.46	(L)	
25		573.35	(D)	+++
26				
27				
28				
28a			(D)	

Table 1
(cont.)

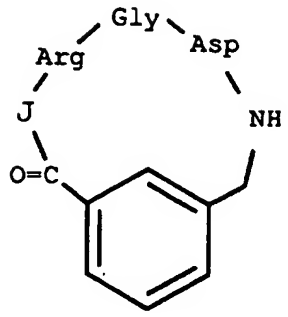
Ex. No.	J	FAB-MS (M+S)	Optical Isomer	IC_{50}
28b			(L)	
28c	$-NHCH_2CH_2C(=O)-$	547.28		+++
28d			(D)	
28e			(L)	

Ex. No.	R^3	R^4	R^5	FAB-MS (M+S)	Optical Isomer	IC_{50}
28f	H	H		639.54	(D)	+++
28g	H	H			(L)	

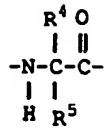
Specifically provided by the present invention are those compounds of Table 1 wherein Asp is replaced by a residue selected from: αMeAsp; βMeAsp; NMeAsp; D-Asp; Asp-(methylcarbonyloxymethyl ester); Asp-(ethylcarbonyloxymethyl ester); Asp-(t-butylcarbonyloxymethyl ester); Asp-(cyclohexylcarbonyloxymethyl ester);

Asp-(1-(methylcarbonyloxy)ethyl ester);
Asp-(1-(ethylcarbonyloxy)ethyl ester);
Asp-(1-(t-butylcarbonyloxy)ethyl ester);
Asp-(1-(cyclohexylcarbonyloxy)ethyl ester);
Asp-(*i*-propyloxycarbonyloxymethyl ester);
Asp-(cyclohexylcarbonyloxymethyl ester);
Asp-(*t*-butyloxycarbonyloxymethyl ester);
Asp-(1-(i-propyloxycarbonyloxy)ethyl ester);
Asp-(1-(cyclohexyloxycarbonyloxy)ethyl ester);
Asp-(1-(*t*-butyloxycarbonyloxy)ethyl ester);
Asp-(dimethylaminoethyl ester);
Asp-(diethylaminoethyl ester);
Asp-((1,3-dioxa-5-methyl-cyclopenten-2-one-4-yl)methyl ester);
Asp-((5-(*t*-butyl)-1,3-dioxa-cyclopenten-2-one-4-yl)methyl ester);
Asp-((1,3-dioxa-5-phenyl-cyclopenten-2-one-4-yl)methyl ester);
Asp-(1-(2-(2-methoxypropyl)carbonyloxy)ethyl ester).

Table 2



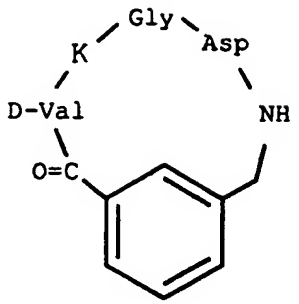
J =



The optical isomer of **J** is indicated.

Ex. No.	R^4	R^5	FAB-MS (M+H)	Optical Isomer	IC_{50}
29	H	H	519.26		++
30	H	CH_3	533.26	(D)	++
31	H	CH_3	533.25	(L)	
32	H	$CH(CH_3)_2$	561.22	(D)	++
32a	H	$CH(CH_3)_2$		(L)	
33	H	$CH_2CH(CH_3)_2$	575.45	(D)	++
33a	H	$CH_2CH(CH_3)_2$		(L)	
34	H	CH_2CH_3	547.21	(D)	++
34a	H	CH_2CH_3		(L)	
35	H	CH_2OH	549.31	(D)	++
35a	H	CH_2OH		(L)	
36	H	phenylmethyl	609.25	(D)	+
37	H	phenylmethyl	609.26	(L)	+

Table 3



K = $-N(R^6)CH(R^7)C(=O)-$

The optical isomer of K is indicated.

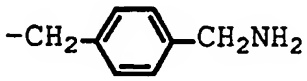
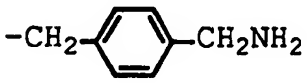
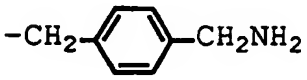
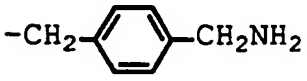
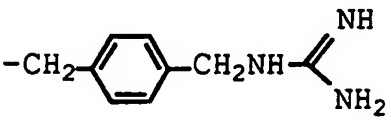
Ex. No.	R^6	R^7	FAB-MS (M+H)	Optical Isomer	IC_{50}
32	H	$-(CH_2)_3NHC(=NH)(NH_2)$	561.22	(L)	++
32a	H	$-(CH_2)_3NHC(=NH)(NH_2)$		(D)	
4	CH_3	$-(CH_2)_3NHC(=NH)(NH_2)$	575.45	(L)	+++
4b	CH_3	$-(CH_2)_3NHC(=NH)(NH_2)$	575.31	(D)	++
38	CH_3	$-(CH_2)_4NHC(=NH)(NH_2)$		(L)	
38a	CH_3	$-(CH_2)_4NHC(=NH)(NH_2)$		(D)	
39	H			(L)	
39a	H			(D)	
40	CH_3		595.23	(L)	+++
40a	CH_3			(D)	
41	CH_3			(L)	

Table 3 (continued)

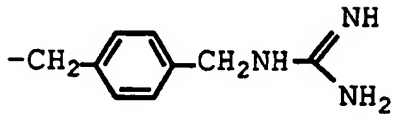
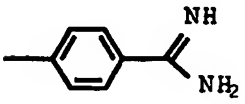
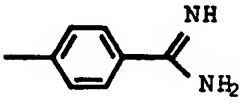
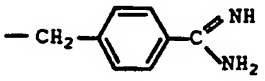
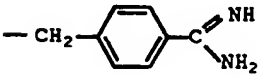
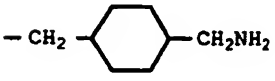
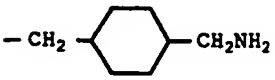
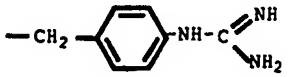
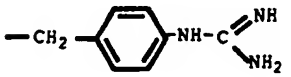
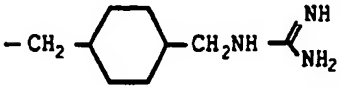
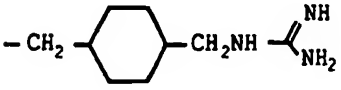
41a	CH_3		(D)
42	CH_3	$-CH_2SCH_2CH_2NH_2$	(L)
42a	CH_3	$-CH_2SCH_2CH_2NH_2$	(D)
43	CH_3	$-CH_2SCH_2CH_2NHC(=NH)(NH_2)$	(L)
43a	CH_3	$-CH_2SCH_2CH_2NHC(=NH)(NH_2)$	(D)
44	CH_3	$-CH_2CH_2SCH_2CH_2NH_2$	(L)
44a	CH_3	$-CH_2CH_2SCH_2CH_2NH_2$	(D)
45	CH_3	$-CH_2CH_2SCH_2CH_2NHC(=NH)(NH_2)$	(L)
45a	CH_3	$-CH_2CH_2SCH_2CH_2NHC(=NH)(NH_2)$	(D)
46	CH_3		(L)
46a	CH_3		(D)
47	CH_3		(L)
47a	CH_3		(D)
48	CH_3		(L)
48b	CH_3		(D)

Table 3 (continued)

Ex. No.	R^6	R^7	FAB-MS (M+H)	Optical Isomer	IC_{50}
48a	CH_3			(L)	
48d	CH_3			(D)	
49	CH_3			(L)	
49a	CH_3			(D)	

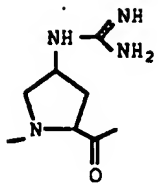
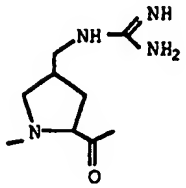
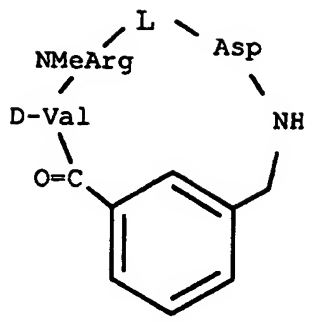
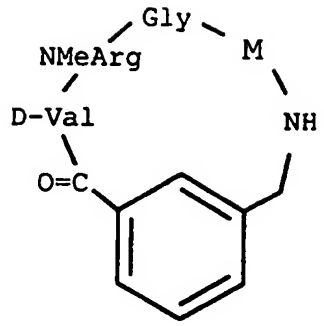
Ex. No.	K	FAB-MS (M+H)
52		
53		

Table 4



Ex. No.	L	FAB-MS (M+H)	Optical Isomer	IC_{50}
4	$-NHCH_2C(=O)-$	575.45		+++
54	$-NHCH_2CH_2C(=O)-$	589.32		++
55	$-OCH_2C(=O)-$			
56	$-OCH_2CH_2C(=O)-$			
57	$-SCH_2C(=O)-$			
58	$-SCH_2CH_2C(=O)-$			
58c	$-NHCH(CH_3)C(=O)-$	589.31	(L)	+

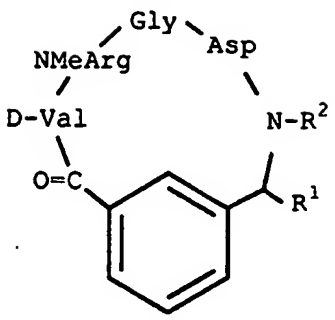
Table 5



M = $-N(R^{10})C(R^8)(R^9)C(=O)-$

Ex. No.	R^8	R^9	R^{10}	FAB-MS (M+H)	Optical Isomer	IC_{50}
4	$-CH_2COOH$	H	H	575.45	(L)	+++
63	$-CH_2COOH$	CH_3	H	589.29	isomer 1	++
63a	$-CH_2COOH$	CH_3	H	589.27	isomer 2	+
64	$-CH(CH_3)COOH$	H	H	589.43	isomer 1	+++
64a	$-CH(CH_3)COOH$	H	H	589.45	isomer 2	+
64b	$-CH_2COOH$	H	CH_3	589.42		++
64c	$-CH_2COOH$	H	H	575.42	(D)	++
66	$-CH_2SO_3H$	H	H			

Table 6



The optical isomer of $-CH(R^1)N(R^2)-$ is indicated.

Ex. No.	R^1	R2	FAB-MS(M+H)	Optical Isomer	IC_{50}
4	H	H	575.45		+++
68	CH_3	H	589.31	isomer 1	+++
68a	CH_3	H	589.31	isomer 2	+++
69	CH_2CH_3	H		R	
69a	CH_2CH_3	H		S	
70	$CH(CH_3)_2$	H		R	
70a	$CH(CH_3)_2$	H		S	
71	$CH_2CH_2CH_3$	H		R	
71a	$CH_2CH_2CH_3$	H		S	
72	$CH_2CH_2CH_2CH_3$	H		R	
72a	$CH_2CH_2CH_2CH_3$	H		S	
73	$C(CH_3)_3$	H		R	
73a	$C(CH_3)_3$	H		S	
74	$CH(CH_3)CH_2CH_3$	H		R	
74a	$CH(CH_3)CH_2CH_3$	H		S	
75	benzyl	H		R	
75a	benzyl	H		S	

Table 6
(continued)

Example No.	R^1	R2	FAB-MS(M+H)	Optical Isomer	
76	phenyl	H	651.33	isomer 1	++
76a	phenyl	H	651.33	isomer 2	++
77	cyclopentyl	H		R	
77a	cyclopentyl	H		S	
78	cyclohexyl	H		R	
78a	cyclohexyl	H		S	
79	H	CH_3	589.33		
80	H	CH_2CH_3			
81	H	$CH_2CH_2CH_3$			
82	H	$CH(CH_3)_2$			
83	H	$CH_2CH_2CH_2CH_3$			
84	H	$C(CH_3)_3$			
85	H	$CH(CH_3)CH_2CH_3$			
86	H	benzyl			

Table 7

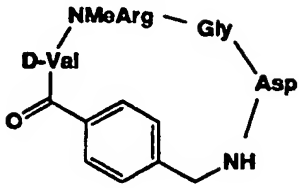
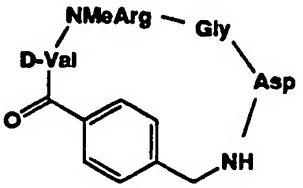
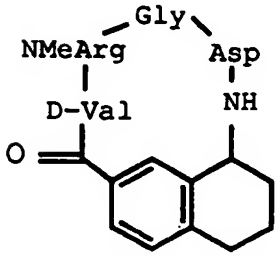
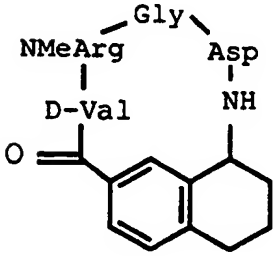
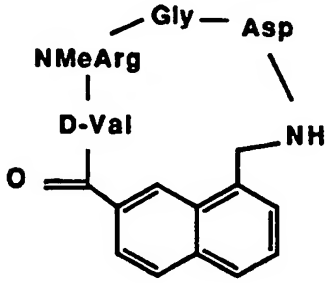
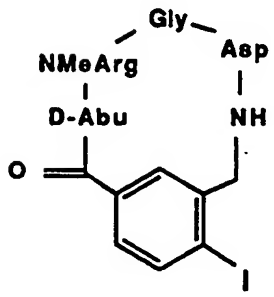
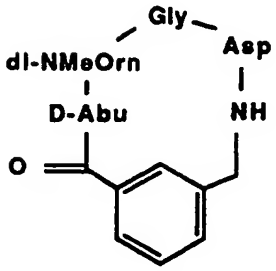
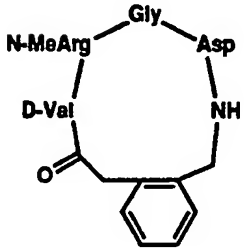
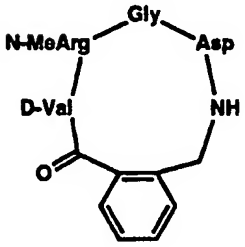
Ex.No.	Structure	FAB-MS (M+H)	IC_{50}
87	 isomer 1	575.41	+++
88	 isomer 2	575.44	+++
89a	 isomer 1	615.34	+++
89b	 isomer 2	615.35	+++
89c		625.32	++

Table 8

Ex. No.	Structure	FAB-MS [M+H]	IC_{50}
89d		687.33	+++
89e		533.34	++
90		589	+++
91		575	+++

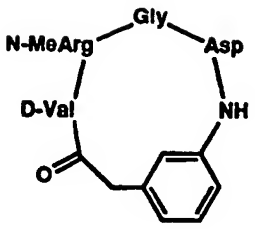
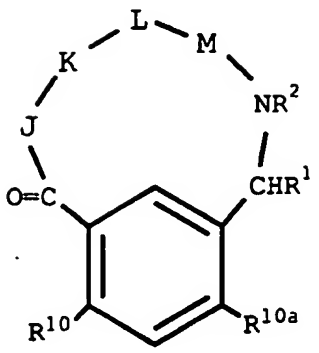
92		575	+++

Table 9



(VII)

wherein **J** = D-Val, **K** = NMeArg, **L** = Gly, **M** = Asp

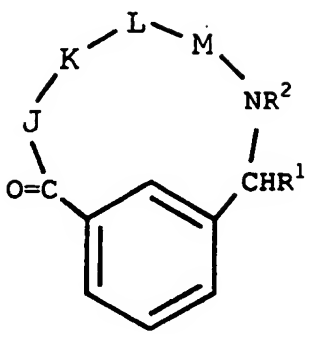
Example Number	R^{10a}	R^{10}	FAB-MS (M+H)	IC_{50}
93	Cl	H	609	+++
94	I	H	701.37	+++
95	MeO	H	623 (+H_2O)	
96	Me	H	589	+++
97	H	Cl	609	+++
98	H	I	701	
99	H	MeO	605	+++
100	H	Me	589	+++

wherein **J** = D-Abu, **K** = NMeArg, **L** = Gly, **M** = Asp

100a	H	Cl	595.4	+++
100b	H	I	687.3	+++
100c	H	Me	575.4	+++

Specifically disclosed by the present invention are those compounds of Tables 3-9 wherein D-Val is replaced by a residue selected from: D-2-aminobutyric acid, D-Leu, D-Ala, Gly, D-Pro, D-Ser, D-Lys, β-Ala, Pro, Phe, NMeGly, D-Nle, D-Phg, D-Ile, D-Phe, D-Tyr, Ala.

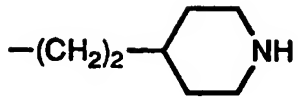
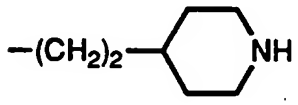
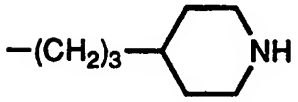
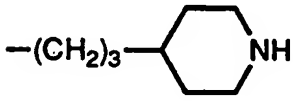
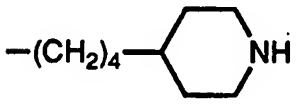
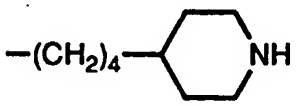
Table 10

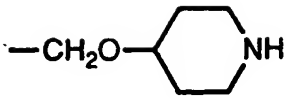
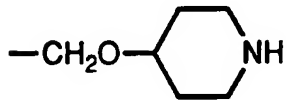
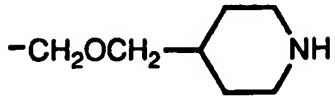
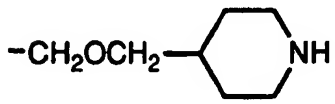
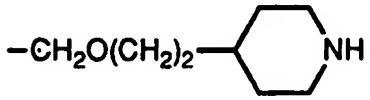
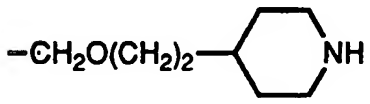
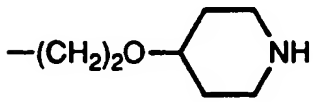
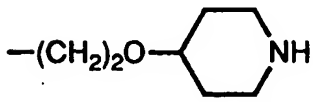
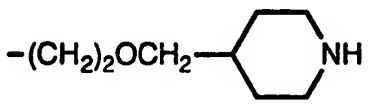
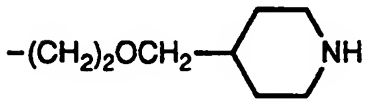


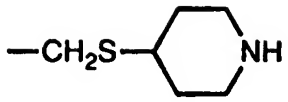
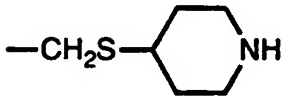
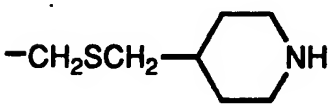
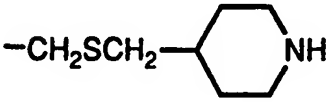
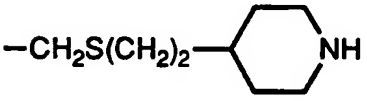
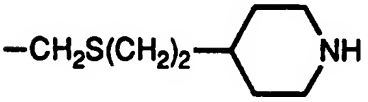
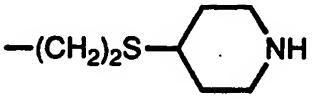
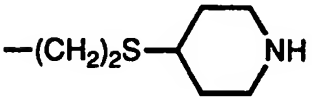
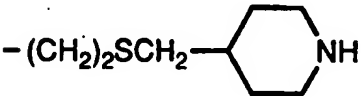
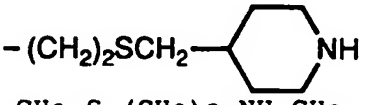
wherein L = Gly, M = Asp, R^2 and R^1 = H,

K = $-N(R^6)CH(R^7)C(=O)-$

J = D-Val

Ex. No.	R^6	R^7	Optical Isomer	IC_{50}
101	CH_3		L	
102	CH_3		D	
103	CH_3		L	
104	CH_3		D	
105	CH_3		L	
106	CH_3		D	

107	CH_3		L
108	CH_3		D
109	CH_3		L
110	CH_3		D
111	CH_3		L
112	CH_3		D
113	CH_3		L
114	CH_3		D
115	CH_3		L
116	CH_3		D

117	CH_3		L
118	CH_3		D
119	CH_3		L
120	CH_3		D
121	CH_3		L
122	CH_3		D
123	CH_3		L
124	CH_3		D
125	CH_3		L
126	CH_3		D
127	CH_3	$-CH_2-S-(CH_2)_3-NH-CH_3$	L
128	CH_3	$-CH_2-S-(CH_2)_3-NH-CH_3$	D

129	CH_3	$-CH_2-S-(CH_2)_3-NH-CH_2CH_3$	L
130	CH_3	$-CH_2-S-(CH_2)_3-NH-CH_2CH_3$	D
131	CH_3	$-CH_2-S-(CH_2)_3-NH-CH(CH_3)_2$	L
132	CH_3	$-CH_2-S-(CH_2)_3-NH-CH(CH_3)_2$	D
133	CH_3	$-CH_2-S-(CH_2)_3-NH-CH_2CH_2-CH_3$	L
134	CH_3	$-CH_2-S-(CH_2)_3-NH-CH_2CH_2-CH_3$	D
135	CH_3	$-CH_2-S-(CH_2)_3-NH-C(CH_3)_3$	L
136	CH_3	$-CH_2-S-(CH_2)_3-NH-C(CH_3)_3$	D
137	CH_3	$CH_2-O-(CH_2)_3-NH-CH_3$	L
138	CH_3	$CH_2-O-(CH_2)_3-NH-CH_3$	D
139	CH_3	$CH_2-O-(CH_2)_3-NH-CH_2CH_3$	L
140	CH_3	$CH_2-O-(CH_2)_3-NH-CH_2CH_3$	D
141	CH_3	$CH_2-O-(CH_2)_3-NH-CH(CH_3)_2$	L
142	CH_3	$CH_2-O-(CH_2)_3-NH-CH(CH_3)_2$	D
143	CH_3	$CH_2-O-(CH_2)_3-NH-CH_2CH_2CH_3$	L
144	CH_3	$CH_2-O-(CH_2)_3-NH-CH_2CH_2CH_3$	D
145	CH_3	$CH_2-O-(CH_2)_3-NH-C(CH_3)_3$	L

146	CH_3	CH_2-O-$(CH_2)_3$-NH-$C(CH_3)_3$	D
147	CH_3	-CH_2-S-$(CH_2)_2$-NH-CH_3	L
148	CH_3	-CH_2-S-$(CH_2)_2$-NH-CH_3	D
149	CH_3	-CH_2-S-$(CH_2)_2$-NH-CH_2CH_3	L
150	CH_3	-CH_2-S-$(CH_2)_2$-NH-CH_2CH_3	D
151	CH_3	-CH_2-S-$(CH_2)_2$-NH-$CH(CH_3)_2$	L
152	CH_3	-CH_2-S-$(CH_2)_2$-NH-$CH(CH_3)_2$	D
153	CH_3	-CH_2-S-$(CH_2)_2$-NH-CH_2CH_2-CH_3	L
154	CH_3	-CH_2-S-$(CH_2)_2$-NH-CH_2CH_2-CH_3	D
155	CH_3	-CH_2-S-$(CH_2)_2$-NH-$C(CH_3)_3$	L
156	CH_3	-CH_2-S-$(CH_2)_2$-NH-$C(CH_3)_3$	D
157	CH_3	CH_2-O-$(CH_2)_2$-NH-CH_3	L
158	CH_3	CH_2-O-$(CH_2)_2$-NH-CH_3	D
159	CH_3	CH_2-O-$(CH_2)_2$-NH-CH_2CH_3	L
160	CH_3	CH_2-O-$(CH_2)_2$-NH-CH_2CH_3	D
161	CH_3	CH_2-O-$(CH_2)_2$-NH-$CH(CH_3)_2$	L
162	CH_3	CH_2-O-$(CH_2)_2$-NH-$CH(CH_3)_2$	D
163	CH_3	CH_2-O-$(CH_2)_2$-NH-$CH_2CH_2CH_3$	L

164	CH_3	CH_2-O-$(CH_2)_2$-NH-$CH_2CH_2CH_3$	D
165	CH_3	CH_2-O-$(CH_2)_2$-NH-$C(CH_3)_3$	L
166	CH_3	CH_2-O-$(CH_2)_2$-NH-$C(CH_3)_3$	D
167	CH_3	-CH_2-S-$(CH_2)_4$-NH-CH_3	L
168	CH_3	-CH_2-S-$(CH_2)_4$-NH-CH_3	D
169	CH_3	-CH_2-S-$(CH_2)_4$-NH-CH_2CH_3	L
170	CH_3	-CH_2-S-$(CH_2)_4$-NH-CH_2CH_3	D
171	CH_3	-CH_2-S-$(CH_2)_4$-NH-$CH(CH_3)_2$	L
172	CH_3	-CH_2-S-$(CH_2)_4$-NH-$CH(CH_3)_2$	D
173	CH_3	-CH_2-S-$(CH_2)_4$-NH-CH_2CH_2-CH_3	L
174	CH_3	-CH_2-S-$(CH_2)_4$-NH-CH_2CH_2-CH_3	D
175	CH_3	-CH_2-S-$(CH_2)_4$-NH-$C(CH_3)_3$	L
176	CH_3	-CH_2-S-$(CH_2)_4$-NH-$C(CH_3)_3$	D
177	CH_3	CH_2-O-$(CH_2)_4$-NH-CH_3	L
178	CH_3	CH_2-O-$(CH_2)_4$-NH-CH_3	D
179	CH_3	CH_2-O-$(CH_2)_4$-NH-CH_2CH_3	L
180	CH_3	CH_2-O-$(CH_2)_4$-NH-CH_2CH_3	D
181	CH_3	CH_2-O-$(CH_2)_4$-NH-$CH(CH_3)_2$	L

182	CH_3	CH_2-O-$(CH_2)_4$-NH-$CH(CH_3)_2$	D
183	CH_3	CH_2-O-$(CH_2)_4$-NH-$CH_2CH_2CH_3$	L
184	CH_3	CH_2-O-$(CH_2)_4$-NH-$CH_2CH_2CH_3$	D
185	CH_3	CH_2-O-$(CH_2)_4$-NH-$C(CH_3)_3$	L
186	CH_3	CH_2-O-$(CH_2)_4$-NH-$C(CH_3)_3$	D
187	CH_3	-CH_2-S-$(CH_2)_5$-NH-CH_3	L
188	CH_3	-CH_2-S-$(CH_2)_5$-NH-CH_3	D
189	CH_3	-CH_2-S-$(CH_2)_5$-NH-CH_2CH_3	L
190	CH_3	-CH_2-S-$(CH_2)_5$-NH-CH_2CH_3	D
191	CH_3	-CH_2-S-$(CH_2)_5$-NH-$CH(CH_3)_2$	L
192	CH_3	-CH_2-S-$(CH_2)_5$-NH-$CH(CH_3)_2$	D
193	CH_3	-CH_2-S-$(CH_2)_5$-NH-CH_2CH_2-CH_3	L
194	CH_3	-CH_2-S-$(CH_2)_5$-NH-CH_2CH_2-CH_3	D
195	CH_3	-CH_2-S-$(CH_2)_5$-NH-$C(CH_3)_3$	L
196	CH_3	-CH_2-S-$(CH_2)_5$-NH-$C(CH_3)_3$	D
197	CH_3	CH_2-O-$(CH_2)_5$-NH-CH_3	L
198	CH_3	CH_2-O-$(CH_2)_5$-NH-CH_3	D
199	CH_3	CH_2-O-$(CH_2)_5$-NH-CH_2CH_3	L

200	CH_3	CH_2-O-$(CH_2)_5$-NH-CH_2CH_3	D
201	CH_3	CH_2-O-$(CH_2)_5$-NH-$CH(CH_3)_2$	L
202	CH_3	CH_2-O-$(CH_2)_5$-NH-$CH(CH_3)_2$	D
203	CH_3	CH_2-O-$(CH_2)_5$-NH-$CH_2CH_2CH_3$	L
204	CH_3	CH_2-O-$(CH_2)_5$-NH-$CH_2CH_2CH_3$	D
205	CH_3	CH_2-O-$(CH_2)_5$-NH-$C(CH_3)_3$	L
206	CH_3	CH_2-O-$(CH_2)_5$-NH-$C(CH_3)_3$	D

207	CH_3	-$(CH_2)_2$-S-$(CH_2)_3$-NH-CH_3	L
208	CH_3	-$(CH_2)_2$-S-$(CH_2)_3$-NH-CH_3	D
209	CH_3	-$(CH_2)_2$-S-$(CH_2)_3$-NH-CH_2CH_3	L
210	CH_3	-$(CH_2)_2$-S-$(CH_2)_3$-NH-CH_2CH_3	D
211	CH_3	-$(CH_2)_2$-S-$(CH_2)_3$-NH-$CH(CH_3)_2$	L
212	CH_3	-$(CH_2)_2$-S-$(CH_2)_3$-NH-$CH(CH_3)_2$	D
213	CH_3	-$(CH_2)_2$-S-$(CH_2)_3$-NH-CH_2CH_2-CH_3	L
214	CH_3	-$(CH_2)_2$-S-$(CH_2)_3$-NH-CH_2CH_2-CH_3	D
215	CH_3	-$(CH_2)_2$-S-$(CH_2)_3$-NH-$C(CH_3)_3$	L
216	CH_3	-$(CH_2)_2$-S-$(CH_2)_3$-NH-$C(CH_3)_3$	D
217	CH_3	-$(CH_2)_2$-O-$(CH_2)_3$-NH-CH_3	L

218	CH_3	$-(CH_2)_2-O-(CH_2)_3-NH-CH_3$	D
219	CH_3	$-(CH_2)_2-O-(CH_2)_3-NH-CH_2CH_3$	L
220	CH_3	$-(CH_2)_2-O-(CH_2)_3-NH-CH_2CH_3$	D
221	CH_3	$-(CH_2)_2-O-(CH_2)_3-NH-CH(CH_3)_2$	L
222	CH_3	$-(CH_2)_2-O-(CH_2)_3-NH-CH(CH_3)_2$	D
223	CH_3	$-(CH_2)_2-O-(CH_2)_3-NH-CH_2CH_2CH_3$	L
224	CH_3	$-(CH_2)_2-O-(CH_2)_3-NH-CH_2CH_2CH_3$	D
225	CH_3	$-(CH_2)_2-O-(CH_2)_3-NH-C(CH_3)_3$	L
226	CH_3	$-(CH_2)_2-O-(CH_2)_3-NH-C(CH_3)_3$	D
227	CH_3	$-(CH_2)_2-S-(CH_2)_2-NH-CH_3$	L
228	CH_3	$-(CH_2)_2-S-(CH_2)_2-NH-CH_3$	D
229	CH_3	$-(CH_2)_2-S-(CH_2)_2-NH-CH_2CH_3$	L
230	CH_3	$-(CH_2)_2-S-(CH_2)_2-NH-CH_2CH_3$	D
231	CH_3	$-(CH_2)_2-S-(CH_2)_2-NH-CH(CH_3)_2$	L
232	CH_3	$-(CH_2)_2-S-(CH_2)_2-NH-CH(CH_3)_2$	D
233	CH_3	$-(CH_2)_2-S-(CH_2)_2-NH-CH_2CH_2-CH_3$	L
234	CH_3	$-(CH_2)_2-S-(CH_2)_2-NH-CH_2CH_2-CH_3$	D
235	CH_3	$-(CH_2)_2-S-(CH_2)_2-NH-C(CH_3)_3$	L
236	CH_3	$-(CH_2)_2-S-(CH_2)_2-NH-C(CH_3)_3$	D

237	CH_3	$-(CH_2)_2-O-(CH_2)_2-NH-CH_3$	L
238	CH_3	$-(CH_2)_2-O-(CH_2)_2-NH-CH_3$	D
239	CH_3	$-(CH_2)_2-O-(CH_2)_2-NH-CH_2CH_3$	L
240	CH_3	$-(CH_2)_2-O-(CH_2)_2-NH-CH_2CH_3$	D
241	CH_3	$-(CH_2)_2-O-(CH_2)_2-NH-CH(CH_3)_2$	L
242	CH_3	$-(CH_2)_2-O-(CH_2)_2-NH-CH(CH_3)_2$	D
243	CH_3	$-(CH_2)_2-O-(CH_2)_2-NH-CH_2CH_2CH_3$	L
244	CH_3	$-(CH_2)_2-O-(CH_2)_2-NH-CH_2CH_2CH_3$	D
245	CH_3	$-(CH_2)_2-O-(CH_2)_2-NH-C(CH_3)_3$	L
246	CH_3	$-(CH_2)_2-O-(CH_2)_2-NH-C(CH_3)_3$	D
247	CH_3	$-(CH_2)_2-S-(CH_2)_4-NH-CH_3$	L
248	CH_3	$-(CH_2)_2-S-(CH_2)_4-NH-CH_3$	D
249	CH_3	$-(CH_2)_2-S-(CH_2)_4-NH-CH_2CH_3$	L
250	CH_3	$-(CH_2)_2-S-(CH_2)_4-NH-CH_2CH_3$	D
251	CH_3	$-(CH_2)_2-S-(CH_2)_4-NH-CH(CH_3)_2$	L
252	CH_3	$-(CH_2)_2-S-(CH_2)_4-NH-CH(CH_3)_2$	D
251	CH_3	$-(CH_2)_2-S-(CH_2)_4-NH-CH_2CH_2-CH_3$	L
254	CH_3	$-(CH_2)_2-S-(CH_2)_4-NH-CH_2CH_2-CH_3$	D
255	CH_3	$-(CH_2)_2-S-(CH_2)_4-NH-C(CH_3)_3$	L

256	CH_3	$-(CH_2)_2-S-(CH_2)_4-NH-C(CH_3)_3$	D
257	CH_3	$-(CH_2)_3-NH-CH_3$	L
258	CH_3	$-(CH_2)_3-NH-CH_3$	D
259	CH_3	$-(CH_2)_3-NH-CH_2CH_3$	L
260	CH_3	$-(CH_2)_3-NH-CH_2CH_3$	D
261	CH_3	$-(CH_2)_3-NH-CH(CH_3)_2$	L
262	CH_3	$-(CH_2)_3-NH-CH(CH_3)_2$	D
263	CH_3	$-(CH_2)_3-NH-CH_2CH_2CH_3$	L
264	CH_3	$-(CH_2)_3-NH-CH_2CH_2CH_3$	D
265	CH_3	$-(CH_2)_3-NH-C(CH_3)_3$	L
266	CH_3	$-(CH_2)_3-NH-C(CH_3)_3$	D
267	CH_3	$-(CH_2)_4-NH-CH_3$	L
268	CH_3	$-(CH_2)_4-NH-CH_3$	D
269	CH_3	$-(CH_2)_4-NH-CH_2CH_3$	L
270	CH_3	$-(CH_2)_4-NH-CH_2CH_3$	D
271	CH_3	$-(CH_2)_4-NH-CH(CH_3)_2$	L
272	CH_3	$-(CH_2)_4-NH-CH(CH_3)_2$	D
273	CH_3	$-(CH_2)_4-NH-CH_2CH_2CH_3$	L
274	CH_3	$-(CH_2)_4-NH-CH_2CH_2CH_3$	D
275	CH_3	$-(CH_2)_4-NH-C(CH_3)_3$	L
276	CH_3	$-(CH_2)_4-NH-C(CH_3)_3$	D
277	CH_3	$-(CH_2)_5-NH-CH_3$	L
278	CH_3	$-(CH_2)_5-NH-CH_3$	D
279	CH_3	$-(CH_2)_5-NH-CH_2CH_3$	L
280	CH_3	$-(CH_2)_5-NH-CH_2CH_3$	D

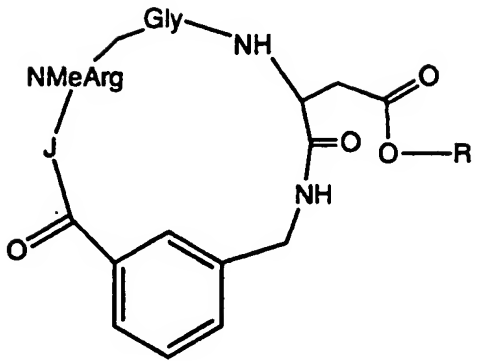
281	CH_3	$-(CH_2)_5-NH-CH(CH_3)_2$	L
282	CH_3	$-(CH_2)_5-NH-CH(CH_3)_2$	D
283	CH_3	$-(CH_2)_5-NH-CH_2CH_2CH_3$	L
284	CH_3	$-(CH_2)_5-NH-CH_2CH_2CH_3$	D
285	CH_3	$-(CH_2)_5-NH-C(CH_3)_3$	L
286	CH_3	$-(CH_2)_5-NH-C(CH_3)_3$	D
287	CH_3	$-(CH_2)_6-NH-CH_3$	L
288	CH_3	$-(CH_2)_6-NH-CH_3$	D
289	CH_3	$-(CH_2)_6-NH-CH_2CH_3$	L
290	CH_3	$-(CH_2)_6-NH-CH_2CH_3$	D
291	CH_3	$-(CH_2)_6-NH-CH(CH_3)_2$	L
292	CH_3	$-(CH_2)_6-NH-CH(CH_3)_2$	D
293	CH_3	$-(CH_2)_6-NH-CH_2CH_2CH_3$	L
294	CH_3	$-(CH_2)_6-NH-CH_2CH_2CH_3$	D
295	CH_3	$-(CH_2)_6-NH-C(CH_3)_3$	L
296	CH_3	$-(CH_2)_6-NH-C(CH_3)_3$	D

Specifically disclosed by the present invention are those compounds of Table 10 wherein D-Val is replaced by a residue selected from: D-2-aminobutyric acid, D-Leu, D-Ala, Gly, D-Pro, D-Ser, D-Lys, β-Ala, Pro, Phe, NMeGly, D-Nle, D-Phg, D-Ile, D-Phe, D-Tyr, Ala.

Also specifically disclosed by the present invention are those compounds of Table 10 wherein Asp is replaced by a residue selected from: αMeAsp; βMeAsp; NMeAsp; D-Asp; Asp-(methylcarbonyloxymethyl ester); Asp-(ethylcarbonyloxymethyl ester); Asp-(t-butylcarbonyloxymethyl ester); Asp-(cyclohexylcarbonyloxymethyl ester);

Asp-(1-(methylcarbonyloxy)ethyl ester);
Asp-(1-(ethylcarbonyloxy)ethyl ester);
Asp-(1-(t-butylcarbonyloxy)ethyl ester);
Asp-(1-(cyclohexylcarbonyloxy)ethyl ester);
Asp-(*i*-propyloxycarbonyloxymethyl ester);
Asp-(cyclohexylcarbonyloxymethyl ester);
Asp-(*t*-butyloxycarbonyloxymethyl ester);
Asp-(1-(i-propyloxycarbonyloxy)ethyl ester);
Asp-(1-(cyclohexyloxycarbonyloxy)ethyl ester);
Asp-(1-(*t*-butyloxycarbonyloxy)ethyl ester);
Asp-(dimethylaminoethyl ester);
Asp-(diethylaminoethyl ester);
Asp-((1,3-dioxa-5-methyl-cyclopenten-2-one-4-yl)methyl ester);
Asp-((5-(*t*-butyl)-1,3-dioxa-cyclopenten-2-one-4-yl)methyl ester);
Asp-((1,3-dioxa-5-phenyl-cyclopenten-2-one-4-yl)methyl ester);
Asp-(1-(2-(2-methoxypropyl)carbonyloxy)ethyl ester).

Table 11



J = D-Abu

Ex. No.	R	FABMS (M+H)
301	$-CH_2-O-C(=O)-CH_3$	633.2
302	$-CH_2-O-C(=O)-CH_2CH_3$	
303	$-CH_2-O-C(=O)-CH(CH_3)_2$	
304	$-CH_2-O-C(=O)-(CH_2)_2-CH_3$	
305	$-CH_2-O-C(=O)-(CH_2)_3-CH_3$	
306	$-CH_2-O-C(=O)-CH_2-CH(CH_3)_2$	
307	$-CH_2-O-C(=O)-CH(CH_3)-CH_2-CH_3$	
308	$-CH_2-O-C(=O)-C(CH_3)_3$	675.3
309	$-CH_2-O-C(=O)$-cyclopropyl	
310	$-CH_2-O-C(=O)$-cyclobutyl	
311	$-CH_2-O-C(=O)$-cyclopentyl	
312	$-CH_2-O-C(=O)$-cyclohexyl	
313	$-CH_2-O-C(=O)$-phenyl	
314	$-CH_2-O-C(=O)$-4-methylphenyl	
315	$-CH_2-O-C(=O)$-4-ethylphenyl	

316 -CH_2-O-C(=O)-4-isopropylphenyl

317 -CH_2-O-C(=O)-4-propylphenyl

318 -CH_2-O-C(=O)-4-t-butylphenyl

319 -CH_2-O-C(=O)-4-methoxyphenyl

320 -CH_2-O-C(=O)-4-ethoxyphenyl

321 -CH_2-O-C(=O)-4-isopropyloxyphenyl

322 -CH_2-O-C(=O)-4-propyloxyphenyl

323 -CH_2-O-C(=O)-4-t-butoxyphenyl

324 -CH_2-O-C(=O)-4-biphenyl

325 -$CH(CH_3)$-O-C(=O)-CH_3

326 -$CH(CH_3)$-O-C(=O)-CH_2CH_3

327 -$CH(CH_3)$-O-C(=O)-$CH(CH_3)_2$

328 -$CH(CH_3)$-O-C(=O)-$(CH_2)_2$-CH_3

329 -$CH(CH_3)$-O-C(=O)-$(CH_2)_3$-CH_3

330 -$CH(CH_3)$-O-C(=O)-CH_2-$CH(CH_3)_2$

331 -$CH(CH_3)$-O-C(=O)-$CH(CH_3)$-CH_2-CH_3

332 -$CH(CH_3)$-O-C(=O)-$C(CH_3)_3$

333 -$CH(CH_3)$-O-C(=O)-cyclopropyl

334 -$CH(CH_3)$-O-C(=O)-cyclobutyl

335 -$CH(CH_3)$-O-C(=O)-cyclopentyl

336 -$CH(CH_3)$-O-C(=O)-cyclohexyl

337 -$CH(CH_3)$-O-C(=O)-phenyl

338 -$CH(CH_3)$-O-C(=O)-4-methylphenyl

339 -$CH(CH_3)$-O-C(=O)-4-ethylphenyl

340 -$CH(CH_3)$-O-C(=O)-4-isopropylphenyl

341 -$CH(CH_3)$-O-C(=O)-4-propylphenyl

342	-CH(CH3)-O-C(=O)-4-t-butylphenyl	
343	-CH(CH3)-O-C(=O)-4-methoxyphenyl	
344	-CH(CH3)-O-C(=O)-4-ethoxyphenyl	
345	-CH(CH3)-O-C(=O)-4-isopropyloxyphenyl	
346	-CH(CH3)-O-C(=O)-4-propyloxyphenyl	
347	-CH(CH3)-O-C(=O)-4-t-butoxyphenyl	
348	-CH(CH3)-O-C(=O)-4-biphenyl	
349	-CH2-O-C(=O)-O-CH3	
350	-CH2-O-C(=O)-O-CH2CH3	
351	-CH2-O-C(=O)-O-CH(CH3)2	667.3
352	-CH2-O-C(=O)-O-(CH2)2-CH3	
353	-CH2-O-C(=O)-O-(CH2)3-CH3	
354	-CH2-O-C(=O)-O-CH2-CH(CH3)2	
355	-CH2-O-C(=O)-O-CH(CH3)-CH2-CH3	
356	-CH2-O-C(=O)-O-C(CH3)3	
357	-CH2-O-C(=O)-O-cyclopropyl	
358	-CH2-O-C(=O)-O-cyclobutyl	
359	-CH2-O-C(=O)-O-cyclopentyl	
360	-CH2-O-C(=O)-O-cyclohexyl	
361	-CH2-O-C(=O)-O-phenyl	
362	-CH2-O-C(=O)-O-4-methylphenyl	
363	-CH2-O-C(=O)-O-4-ethylphenyl	
364	-CH2-O-C(=O)-O-4-isopropylphenyl	
365	-CH2-O-C(=O)-O-4-propylphenyl	
366	-CH2-O-C(=O)-O-4-t-butylphenyl	

367 $-CH_2-O-C(=O)-O-4$-methoxyphenyl

368 $-CH_2-O-C(=O)-O-4$-ethoxyphenyl

369 $-CH_2-O-C(=O)-O-4$-isopropyloxyphenyl

370 $-CH_2-O-C(=O)-O-4$-propyloxyphenyl

371 $-CH_2-O-C(=O)-O-4-t$-butoxyphenyl

372 $-CH_2-O-C(=O)-O-4$-biphenyl

373 $-CH(CH_3)-O-C(=O)-O-CH_3$

374 $-CH(CH_3)-O-C(=O)-O-CH_2CH_3$

375 $-CH(CH_3)-O-C(=O)-O-CH(CH_3)_2$

376 $-CH(CH_3)-O-C(=O)-O-(CH_2)_2-CH_3$

377 $-CH(CH_3)-O-C(=O)-O-(CH_2)_3-CH_3$

378 $-CH(CH_3)-O-C(=O)-O-CH_2-CH(CH_3)_2$

379 $-CH(CH_3)-O-C(=O)-O-CH(CH_3)-CH_2-CH_3$

380 $-CH(CH_3)-O-C(=O)-O-C(CH_3)_3$

381 $-CH(CH_3)-O-C(=O)-O$-cyclopentyl

382 $-CH(CH_3)-O-C(=O)-O$-cyclobutyl

383 $-CH(CH_3)-O-C(=O)-O$-cyclopentyl

384 $-CH(CH_3)-O-C(=O)-O$-cyclohexyl

385 $-CH(CH_3)-O-C(=O)-O$-phenyl

386 $-CH(CH_3)-O-C(=O)-O-4$-methylphenyl

387 $-CH(CH_3)-O-C(=O)-O-4$-ethylphenyl

388 $-CH(CH_3)-O-C(=O)-O-4$-isopropylphenyl

389 $-CH(CH_3)-O-C(=O)-O-4$-propylphenyl

390 $-CH(CH_3)-O-C(=O)-O-4-t$-butylphenyl

391 -CH(CH$_3$)-O-C(=O)-O-4-methoxyphenyl

392 -CH(CH$_3$)-O-C(=O)-O-4-ethoxyphenyl

393 -CH(CH$_3$)-O-C(=O)-O-4-isopropyloxyphenyl

394 -CH(CH$_3$)-O-C(=O)-O-4-propyloxyphenyl

395 -CH(CH$_3$)-O-C(=O)-O-4-t-butoxyphenyl

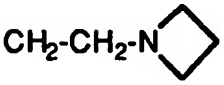
396 -CH(CH$_3$)-O-C(=O)-O-4-biphenyl

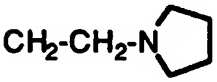
397 CH_2-N(CH$_3$)$_2$

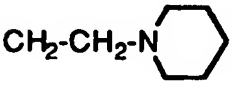
398 CH_2-N(CH_2-CH$_3$)$_2$

399 CH_2CH_2-N(CH$_3$)$_2$

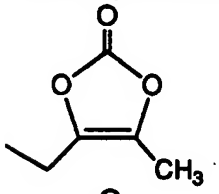
400 CH_2-CH_2-N(CH_2CH_3)$_2$

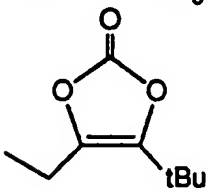
401 

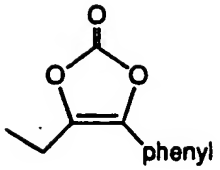
402 

403 

404 -CH(CH$_3$)OC(=O)C(CH$_3$)$_2$OCH$_3$

405 

406 

407 

408 $CH_2C(=O)OCH_3$

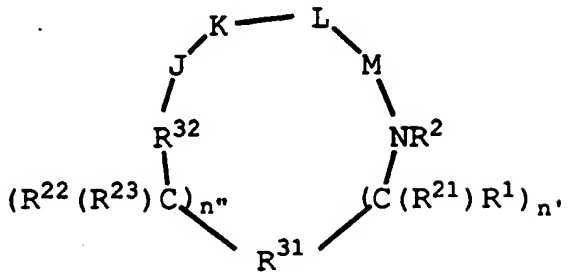
409 $CH_2C(=O)O$-tBu

Specifically disclosed by the present invention are those compounds of Table 10 wherein D-Abu is replaced by a residue selected from: D-Val, D-Leu, D-Ala, Gly, D-Pro, D-norvaline, D-Ser, D-Lys, β-Ala, Pro, Phe, NMeGly, D-Nle, D-Phg, D-Ile, D-Phe, D-Tyr, Ala.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt or prodrug form thereof wherein:

R^{31} is a C_6-C_{14} saturated, partially saturated, or aromatic carbocyclic ring system substituted with 0-4 R^{10} or R^{10a};

R^{32} is selected from:
-C(=O)-;
-C(=S)-
$-S(=O)_2-$;
-S(=O)-;
$-P(=Z)(ZR^{13})-$;

Z is S or O;

n" and n' are independently 0-2;

R^1 and R^{22} are independently selected from the following groups:

hydrogen,
C_1-C_8 alkyl substituted with 0-2 R^{11};
C_2-C_8 alkenyl substituted with 0-2 R^{11};
C_2-C_8 alkynyl substituted with 0-2 R^{11};
C_3-C_{10} cycloalkyl substituted with 0-2 R^{11};

aryl substituted with 0-2 R^{12};

a 5-10-membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, said heterocyclic ring being substituted with 0-2 R^{12};

=O, F, Cl, Br, I, $-CF_3$, -CN, $-CO_2R^{13}$, $-C(=O)R^{13}$, $-C(=O)N(R^{13})_2$, -CHO, $-CH_2OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{14}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{14}SO_2N(R^{13})_2$, $-NR^{14}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-SR^{13}$, $-S(=O)R^{13a}$, $-SO_2N(R^{13})_2$, $-N(R^{13})_2$, $-NHC(=NH)NHR^{13}$, $-C(=NH)NHR^{13}$, $=NOR^{13}$, NO_2, $-C(=O)NHOR^{13}$, $-C(=O)NHNR^{13}R^{13a}$, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy;

R^1 and R^{21} can alternatively join to form a 3-7 membered carbocyclic ring substituted with 0-2 R^{12};

when n' is 2, R^1 or R^{21} can alternatively be taken together with R^1 or R^{21} on an adjacent carbon atom to form a direct bond, thereby to form a double or triple bond between said carbon atoms;

R^{22} and R^{23} can alternatively join to form a 3-7 membered carbocyclic ring substituted with 0-2 R^{12};

when n" is 2, R^{22} or R^{23} can alternatively be taken together with R^{22} or R^{23} on an adjacent carbon atom

to form a direct bond, thereby to form a double or triple bond between the adjacent carbon atoms;

R^1 and R^2, where R^{21} is H, can alternatively join to form a 5-8 membered carbocyclic ring substituted with 0-2 R^{12};

R^{11} is selected from one or more of the following:

=O, F, Cl, Br, I, $-CF_3$, $-CN$, $-CO_2R^{13}$, $-C(=O)R^{13}$, $-C(=O)N(R^{13})_2$, $-CHO$, $-CH_2OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{14}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{14}SO_2N(R^{13})_2$, $-NR^{14}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-SR^{13}$, $-S(=O)R^{13a}$, $-SO_2N(R^{13})_2$, $-N(R^{13})_2$, $-NHC(=NH)NHR^{13}$, $-C(=NH)NHR^{13}$, $=NOR^{13}$, NO_2, $-C(=O)NHOR^{13}$, $-C(=O)NHNR^{13}R^{13a}$, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy,

C_1-C_5 alkyl, C_2-C_4 alkenyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_2-C_6 alkoxyalkyl, C_3-C_6 cycloalkoxy, C_1-C_4 alkyl (alkyl being substituted with 1-5 groups selected independently from: $-NR^{13}R^{14}$, $-CF_3$, NO_2, $-SO_2R^{13a}$, or $-S(=O)R^{13a}$),

aryl substituted with 0-2 R^{12},

a 5-10-membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, and O, said heterocyclic ring being substituted with 0-2 R^{12};

R^{12} is selected from one or more of the following:

phenyl, benzyl, phenethyl, phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_7-C_{10} arylalkyl, C_1-C_5 alkoxy, $-CO_2R^{13}$, $-C(=O)NHOR^{13a}$, $-C(=O)NHN(R^{13})_2$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, C_3-C_6 cycloalkoxy, $-OC(=O)R^{13}$, $-C(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-(C_1$-C_4 alkyl$)-OR^{13}$, $-N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{13}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}SO_2N(R^{13})_2$, $-NR^{13}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-S(=O)R^{13a}$, $-SR^{13}$, $-SO_2N(R^{13})_2$, C_2-C_6 alkoxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, C_1-C_4 alkyl (alkyl being substituted with $-N(R^{13})_2$, $-CF_3$, NO_2, or $-S(=O)R^{13a}$);

R^{13} is selected independently from: H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, $-(C_1$-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

R^{13a} is C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, $-(C_1$-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

when two R^{13} groups are bonded to a single N, said R^{13} groups may alternatively be taken together to form $-(CH_2)_{2-5}-$ or $-(CH_2)O(CH_2)-$;

R^{14} is OH, H, C_1-C_4 alkyl, or benzyl;

R^{21} and R^{23} are independently selected from:

hydrogen;

C_1-C_4 alkyl, optionally substituted with 1-6 halogen;
benzyl;

R^2 is H or C_1-C_8 alkyl;

R^{10} and R^{10a} are selected independently from one or more of the following:

phenyl, benzyl, phenethyl, phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_7-C_{10} arylalkyl, C_1-C_6 alkoxy, $-CO_2R^{13}$, $-C(=O)NHOR^{13a}$, $-C(=O)N(R^{13})_2$, $-C(=O)NHN(R^{13})_2$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, C_3-C_6 cycloalkoxy, $-OC(=O)R^{13}$, $-C(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-(C_1$-C_4 alkyl$)-OR^{13}$, $-N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{13}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}SO_2N(R^{13})_2$, $-NR^{13}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-S(=O)R^{13a}$, $-SR^{13}$, $-SO_2N(R^{13})_2$, C_2-C_6 alkoxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, C_1-C_4 alkyl (alkyl being substituted with $-N(R^{13})_2$, $-CF_3$, NO_2, or $-S(=O)R^{13a}$);

J is β-Ala or an L-isomer or D-isomer amino acid of structure $-N(R^3)C(R^4)(R^5)C(=O)-$, wherein:

R^3 is H or C_1-C_8 alkyl;

R^4 is H or C_1-C_3 alkyl;

R^5 is selected from:
hydrogen;

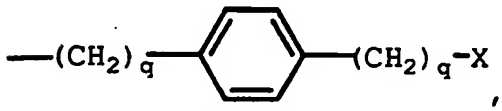
C_1-C_8 alkyl substituted with 0-2 R^{11};
C_2-C_8 alkenyl substituted with 0-2 R^{11};
C_2-C_8 alkynyl substituted with 0-2 R^{11};
C_3-C_{10} cycloalkyl substituted with 0-2 R^{11};

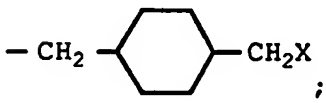
aryl substituted with 0-2 R^{12};

a 5-10-membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, or O, said heterocyclic ring being substituted with 0-2 R^{12};

=O, F, Cl, Br, I, $-CF_3$, $-CN$, $-CO_2R^{13}$, $-C(=O)R^{13}$, $-C(=O)N(R^{13})_2$, $-CHO$, $-CH_2OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{14}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{14}SO_2N(R^{13})_2$, $-NR^{14}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-SR^{13}$, $-S(=O)R^{13a}$, $-SO_2N(R^{13})_2$, $-N(R^{13})_2$, $-NHC(=NH)NHR^{13}$, $-C(=NH)NHR^{13}$, $=NOR^{13}$, NO_2, $-C(=O)NHOR^{13}$, $-C(=O)NHNR^{13}R^{13a}$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, $-SC(=NH)NHR^{13}$, N_3, $-Si(CH_3)_3$, (C_1-C_5 alkyl)NHR^{16};

-(C_0-C_6 alkyl)X;

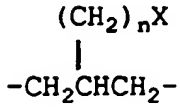

, where q is independently 0,1;


;

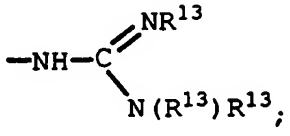
$-(CH_2)_mS(O)_{p'}(CH_2)_2X$, where m = 1,2 and p' = 0-2;

wherein X is defined below; and

R^3 and R^4 may also be taken together to form



where n = 0,1 and X is



R^3 and R^5 can alternatively be taken together to form $-(CH_2)_t-$ or $-CH_2S(O)_{p'}C(CH_3)_2-$, where t = 2-4 and p' = 0-2; or

R^4 and R^5 can alternatively be taken together to form $-(CH_2)_u-$, where u = 2-5;

R^{16} is selected from:

an amine protecting group;

1-2 amino acids;

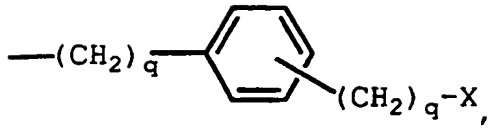
1-2 amino acids substituted with an amine protecting group;

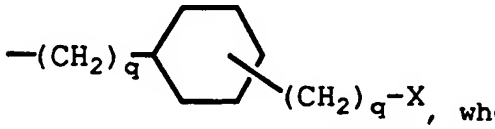
K is a D-isomer or L-isomer amino acid of structure $-N(R^6)CH(R^7)C(=O)-$, wherein:

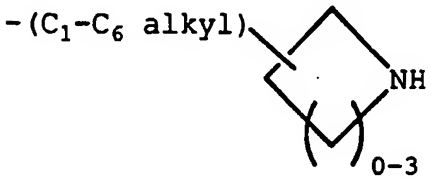
R^6 is H or C_1-C_8 alkyl;

R^7 is selected from:

$-(C_1$-C_7 alkyl)X;


, wherein each q is independently 0-2 and substitution on the phenyl is at the 3 or 4 position;

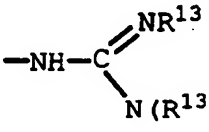

, wherein each q is independently 0-2 and substitution on the cyclohexyl is at the 3 or 4 position;



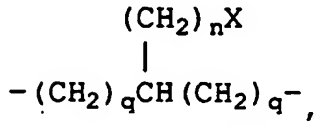
$-(CH_2)_mO-(C_1-C_4$ alkyl)-X, where m = 1 or 2;

$-(CH_2)_mS(O)_{p'}-(C_1-C_4$ alkyl)-X, where m = 1 or 2 and p' = 0-2; and

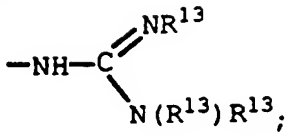
X is selected from:


; $-N(R^{13})R^{13}$; $-C(=NH)(NH_2)$; $-SC(=NH)-NH_2$; $-NH-C(=NH)(NHCN)$; $-NH-C(=NCN)(NH_2)$; $-NH-C(=N-OR^{13})(NH_2)$;

R^6 and R^7 can alternatively be taken together to form


, wherein each q is independently 1 or 2 and wherein

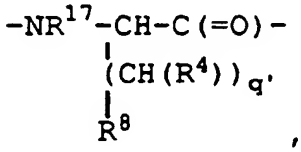
n = 0 or 1 and X is $-NH_2$ or



L is $-Y(CH_2)_vC(=O)-$, wherein:

Y is NH, $N(C_1-C_3$ alkyl), O, or S; and v = 1 or 2;

M is a D-isomer or L-isomer amino acid of structure



, wherein:

q' is 0-2;

R^{17} is H, C_1-C_3 alkyl;

R^8 is selected from:

$-CO_2R^{13}$, $-SO_3R^{13}$, $-SO_2NHR^{14}$, $-B(R^{34})(R^{35})$, $-NHSO_2CF_3$, $-CONHNHSO_2CF_3$, $-PO(OR^{13})_2$, $-PO(OR^{13})R^{13}$, $-SO_2NH$-heteroaryl (said heteroaryl being 5-10-membered and having 1-4 heteroatoms selected independently from N, S, or O) , $-SO_2NHCOR^{13}$, $-CONHSO_2R^{13a}$, $-CH_2CONHSO_2R^{13a}$, $-NHSO_2NHCOR^{13a}$, $-NHCONHSO_2R^{13a}$, $-SO_2NHCONHR^{13}$, $-CO_2R^{13b}$;

R^{34} and R^{35} are independently selected from:

-OH,

-F,

$-N(R^{13})_2$, or

C_1-C_8-alkoxy;

R^{34} and R^{35} can alternatively be taken together form:

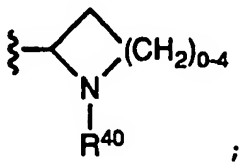
a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;

a divalent cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;

a cyclic boron amide-ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;

R^{13b} is selected from:

(a) C_1-C_8 alkyl;
(b) C_2-C_8 alkenyl;
(c) C_2-C_8 alkynyl;
(d) C_3-C_8 cycloalkyl;
(e) C_1-C_8 alkyl substituted with
  (i) aryl, optionally substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1-C_5$ alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);
  (ii) C_3-C_8 cycloalkyl;
  (iii)



;

(f) aryl, optionally substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1$-C_5 alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(g) C_2-C_8 alkyl, alkenyl or alkynyl; substituted with 1-2 substituents independently selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, phenoxy, benzyloxy, halogen, NO_2, CN, CO_2R^{13}, $CON(R^{13})_2$, $N(R^{36})COR^{36}$, morpholino, 2-(1-morpholino)ethoxy, $N(R^{13})_2$, $N^+(R^{13})_3$, OCOCH3, CF_3, $S(O)_{0-2}R^{13a}$;

(h) $CH(R^{36})OR^{38}$;

(i) $CH(R^{36})OC(=O)R^{37}$;

(j) $CH(R^{36})OC(=O)OR^{38}$;

(k) $CH(R^{36})OC(=O)N(R^{37})_2$;

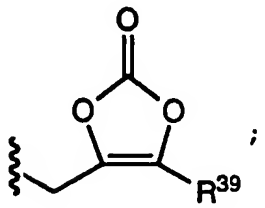
(l) $CH(R^{36})N(R^{36})C(=O)R^{36}$;

(m) $CH(R^{36})CO_2R^{37}$;

(n) $CH(R^{36})CON(R^{13})_2$;

(o) $CH(R^{36})N(R^{13})_2$;

(q)



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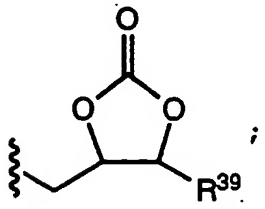
(r)



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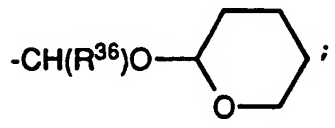
(s)



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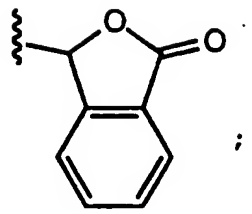

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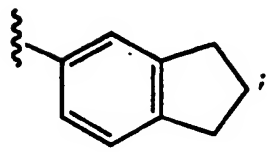
(u)



;

R^{36} is selected independently from: H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, phenyl, or benzyl;

R^{37} is selected from:

(a) H;

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{38} is selected from:

(a) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
(i) C_1-C_4 alkyl;
(ii) C_3-C_8 cycloalkyl;
(iii) C_1-C_5 alkoxy;
(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(b) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{39} is selected from:

(a) H

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
(i) C_1-C_6 alkyl;
(ii) C_1-C_6 alkoxy;
(iii) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$,

$-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{40} is selected from: H, C_1-C_5 alkyl, or benzyl;

provided that at least one of the following conditions is met:

(1) R^{32} is not $-C(=O)-$; or

(2) p' is not 0; or

(3) q' is not 0; or

(4) q is not 0-1; or

(5) X is $-NH-C(=NH)NHCN$, $-NH-C(=NCN)(NH_2)$ or $-NH-C(=NOR^{13})NH_2$; or

(5) R^8 is $-B(R^{34})(R^{35})$ or $-CO_2R^{13b}$.

2. A compound of Claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, wherein:

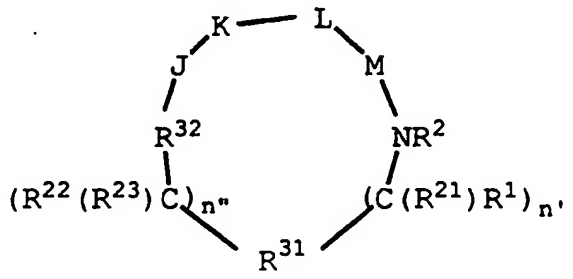
R^{31} is bonded to $(C(R^{23})R^{22})_{n"}$ and $(C(R^{21})R^1)_{n'}$ at 2 different atoms on said carbocyclic ring.

3. A compound of Claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, wherein:

n" is 0 and n' is 0;
n" is 0 and n' is 1;
n" is 0 and n' is 2;
n" is 1 and n' is 0;
n" is 1 and n' is 1;
n" is 1 and n' is 2;
n" is 2 and n' is 0;
n" is 2 and n' is 1; or
n" is 2 and n' is 2.

4. A compound of Claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, wherein: R^6 is methyl, ethyl, or propyl.

5. A compound of Claim 1 of the formula:



(I)

or a pharmaceutically acceptable salt or prodrug form thereof wherein:

R^{31} is a C_6-C_{14} saturated, partially saturated, or aromatic carbocyclic ring system substituted with 0-4 R^{10} or R^{10a};

R^{32} is selected from:
-C(=O)-;
-C(=S)-
-S(=O)$_2$-;

n" and n' are independently 0-2;

R^1 and R^{22} are independently selected from the following groups:

hydrogen,
C_1-C_8 alkyl substituted with 0-2 R^{11},
C_2-C_8 alkenyl substituted with 0-2 R^{11},
C_2-C_8 alkynyl substituted with 0-2 R^{11},

C_3-C_8 cycloalkyl substituted with 0-2 R^{11},
C_6-C_{10} bicycloalkyl substituted with 0-2 R^{11},

aryl substituted with 0-2 R^{12},

a 5-10-membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, or O, said heterocyclic ring being substituted with 0-2 R^{12};

=O, F, Cl, Br, I, $-CF_3$, -CN, $-CO_2R^{13}$, $-C(=O)R^{13}$, $-C(=O)N(R^{13})_2$, -CHO, $-CH_2OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{14}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{14}SO_2N(R^{13})_2$, $-NR^{14}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-SR^{13}$, $-S(=O)R^{13a}$, $-SO_2N(R^{13})_2$, $-CH_2N(R^{13})_2$, $-N(R^{13})_2$, $-NHC(=NH)NHR^{13}$, $-C(=NH)NHR^{13}$, NO_2;

R^1 and R^{21} can alternatively join to form a 5-7 membered carbocyclic ring substituted with 0-2 R^{12};

when n' is 2, R^1 or R^{21} can alternatively be taken together with R^1 or R^{21} on an adjacent carbon atom to form a direct bond, thereby to form a double or triple bond between said carbon atoms;

R^{22} and R^{23} can alternatively join to form a 3-7 membered carbocyclic ring substituted with 0-2 R^{12};

when n" is 2, R^{22} or R^{23} can alternatively be taken together with R^{22} or R^{23} on an adjacent carbon atom to form a direct bond, thereby to form a double or triple bond between said carbon atoms;

R^1 and R^2, where R^{21} is H, can alternatively join to form a 5-8 membered carbocyclic ring substituted with 0-2 R^{12};

R^{11} is selected from one or more of the following:

=O, F, Cl, Br, I, $-CF_3$, $-CN$, $-CO_2R^{13}$, $-C(=O)R^{13}$, $-C(=O)N(R^{13})_2$, $-CHO$, $-CH_2OR^{13}$, $-OC(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{14}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{14}SO_2N(R^{13})_2$, $-NR^{14}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-SR^{13}$, $-S(=O)R^{13a}$, $-SO_2N(R^{13})_2$, $-CH_2N(R^{13})_2$, $-N(R^{13})_2$, $-NHC(=NH)NHR^{13}$, $-C(=NH)NHR^{13}$, $=NOR^{13}$, NO_2;

C_1-C_5 alkyl, C_2-C_4 alkenyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_2-C_6 alkoxyalkyl, C_1-C_4 alkyl (substituted with $-NR^{13}R^{14}$, $-CF_3$, NO_2, $-SO_2R^{13}$, or $-S(=O)R^{13a}$),

aryl substituted with 0-2 R^{12},

a 5-10-membered heterocyclic ring system containing 1-4 heteroatoms independently selected from N, S, or O, said heterocyclic ring being substituted with 0-2 R^{12};

R^{12} is selected from one or more of the following:

phenyl, benzyl, phenethyl, phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_7-C_{10} arylalkyl, C_1-C_5 alkoxy, $-CO_2R^{13}$, $-C(=O)NHOR^{13a}$, $-C(=O)NHN(R^{13})_2$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, C_3-C_6 cycloalkoxy, $-OC(=O)R^{13}$, $-C(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-(C_1$-C_4 alkyl$)$-OR^{13}, $-N(R^{13})_2$,

$-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{13}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}SO_2N(R^{13})_2$, $-NR^{13}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-S(=O)R^{13a}$, $-SR^{13}$, $-SO_2N(R^{13})_2$, C_2-C_6 alkoxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, C_1-C_4 alkyl (alkyl being substituted with $-N(R^{13})_2$, $-CF_3$, NO_2, or $-S(=O)R^{13a}$);

R^{13} is selected independently from: H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, $-(C_1$-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

R^{13a} is C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, $-(C_1$-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

when two R^{13} groups are bonded to a single N, said R^{13} groups may alternatively be taken together to form $-(CH_2)_{2-5}-$ or $-(CH_2)O(CH_2)-$;

R^{14} is OH, H, C_1-C_4 alkyl, or benzyl;

R^{21} and R^{23} are independently selected from:

hydrogen;
C_1-C_4 alkyl, optionally substituted with 1-6 halogen;
benzyl;

R^2 is H or C_1-C_8 alkyl;

R^{10} and R^{10a} are selected independently from one or more of the following:

phenyl, benzyl, phenethyl, phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_7-C_{10} arylalkyl, C_1-C_5 alkoxy, $-CO_2R^{13}$, $-C(=O)NHOR^{13a}$, $-C(=O)NHN(R^{13})_2$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, C_3-C_6 cycloalkoxy, $-OC(=O)R^{13}$, $-C(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-(C_1$-C_4 alkyl$)-OR^{13}$, $-N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{13}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}SO_2N(R^{13})_2$, $-NR^{13}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-S(=O)R^{13a}$, $-SR^{13}$, $-SO_2N(R^{13})_2$, C_2-C_6 alkoxyalkyl, methylenedioxy, ethylenedioxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, C_1-C_4 alkyl (alkyl being substituted with $-N(R^{13})_2$, $-CF_3$, NO_2, or $-S(=O)R^{13a}$);

J is β-Ala or an L-isomer or D-isomer amino acid of structure $-N(R^3)C(R^4)(R^5)C(=O)-$, wherein:

R^3 is H or CH_3;

R^4 is H or C_1-C_3 alkyl;

R^5 is H, C_1-C_8 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_1-C_6 cycloalkylethyl, phenyl, phenylmethyl, CH_2OH, CH_2SH, CH_2OCH_3, CH_2SCH_3, $CH_2CH_2SCH_3$, $(CH_2)_sNH_2$, $(CH_2)_sNHC(=NH)(NH_2)$, $(CH_2)_sNHR^{16}$, where s = 3-5;

R^3 and R^5 can alternatively be taken together to form $-(CH_2)_t-$ (t = 2-4) or $-CH_2SC(CH_3)_2-$; or

R^4 and R^5 can alternatively be taken together to form $-(CH_2)_u-$, where u = 2-5;

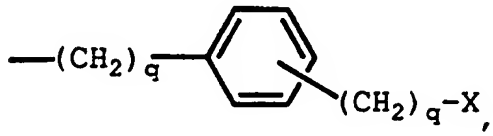
R^{16} is selected from:
an amine protecting group;
1-2 amino acids;
1-2 amino acids subtituted with an amine protecting group;

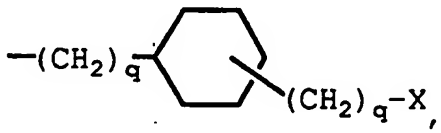
K is a D-isomer or L-isomer amino acid of structure $-N(R^6)CH(R^7)C(=O)-$, wherein:

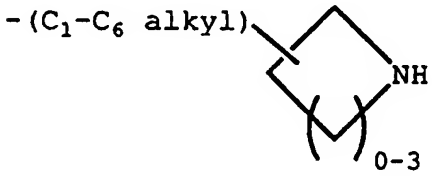
R^6 is H or C_1-C_8 alkyl;

R^7 is selected from:

$-(C_1-C_7$ alkyl)X;


, wherein each q is independently 0-2 and substitution on the phenyl is at the 3 or 4 position;


, wherein each q is independently 0-2 and substitution on the cyclohexyl is at the 3 or 4 position;

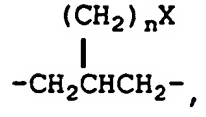


$-(CH_2)_mO-(C_1-C_4$ alkyl$)-X$, where m = 1 or 2;

$-(CH_2)_mS-(C_1-C_4$ alkyl$)-X$, where m = 1 or 2; and

X is selected from:
$-NH-C(=NH)(NH_2)$, $-NHR^{13}$, $-C(=NH)(NH_2)$,
$-SC(NH)-NH_2$;

R^6 and R^7 can alternatively be taken together to form

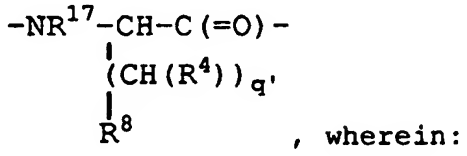


where
n = 0 or 1 and X is $-NH_2$ or $-NH-C(=NH)(NH_2)$;

L is $-Y(CH_2)_vC(=O)-$, wherein:

Y is NH, $N(C_1-C_3$ alkyl$)$, O, or S; and v = 1 or 2;

M is a D-isomer or L-isomer amino acid of structure



, wherein:

q' is 0-2;

R^{17} is H, C_1-C_3 alkyl;

R^8 is selected from:
$-CO_2R^{13}$, $-SO_3R^{13}$, $-SO_2NHR^{14}$, $-B(R^{34})(R^{35})$, $-NHSO_2CF_3$,
$-CONHNHSO_2CF_3$, $-PO(OR^{13})_2$, $-PO(OR^{13})R^{13}$,
$-SO_2NH-$heteroaryl (said heteroaryl being
5-10-membered and having 1-4 heteroatoms selected
independently from N, S, or O) , $-SO_2NH-$heteroaryl

(said heteroaryl being 5-10-membered and having 1-4 heteroatoms selected independently from N, S, or O), $-SO_2NHCOR^{13}$, $-CONHSO_2R^{13a}$, $-CH_2CONHSO_2R^{13a}$, $-NHSO_2NHCOR^{13a}$, $-NHCONHSO_2R^{13a}$, $-SO_2NHCONHR^{13}$, $-CO_2R^{13b}$;

R^{34} and R^{35} are independently selected from:
-OH,
-F,
$-NR^{13}R^{14}$, or
C_1-C_8-alkoxy;

R^{34} and R^{35} can alternatively be taken together form:
a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;
a divalent cyclic boron amide where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;
a cyclic boron amide-ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, 1-4 heteroatoms independently selected from N, S, or O;

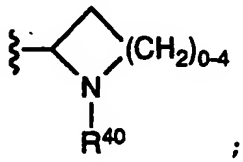
R^{13b} is selected from:

(a) C_1-C_8 alkyl;
(b) C_2-C_8 alkenyl;
(c) C_2-C_8 alkynyl;
(d) C_3-C_8 cycloalkyl;
(e) C_1-C_8 alkyl substituted with
(i) aryl, optionally substituted with 1-2 substituents independently selected

from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1-C_5$ alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(ii) C_3-C_8 cycloalkyl;

(iii)



;

(f) aryl, optionally substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1-C_5$ alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(g) C_2-C_8 alkyl, alkenyl or alkynyl; substituted with 1-2 substituents independently selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, phenoxy, benzyloxy, halogen, NO_2, CN, CO_2R^{13}, $CON(R^{13})_2$, $N(R^{36})COR^{36}$, morpholino, 2-(1-morpholino)ethoxy, $N(R^{13})_2$, $N^+(R^{13})_3$, OCOCH3, CF_3, $S(O)_{0-2}R^{13a}$;

(h) $CH(R^{36})OR^{38}$;

(i) $CH(R^{36})OC(=O)R^{37}$;

(j) $CH(R^{36})OC(=O)OR^{38}$;

(k) $CH(R^{36})OC(=O)N(R^{37})_2$;

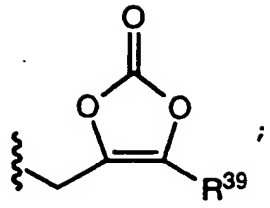
(l) $CH(R^{36})N(R^{36})C(=O)R^{36}$;

(m) $CH(R^{36})CO_2R^{37}$;

(n) $CH(R^{36})CON(R^{13})_2$;

(o) $CH(R^{36})N(R^{13})_2$;

(q)



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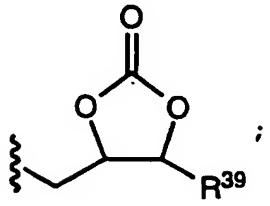

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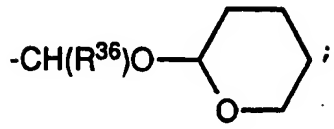

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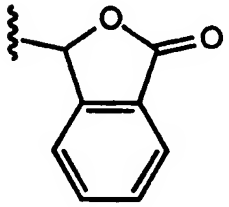

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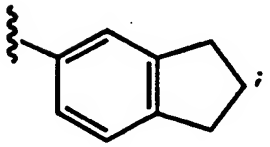


R^{36} is selected independently from: H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, phenyl, or benzyl;

R^{37} is selected from:

(a) H;

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{38} is selected from:

(a) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(b) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{39} is selected from:

(a) H

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:
(i) C_1-C_6 alkyl;
(ii) C_1-C_6 alkoxy;
(iii) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{40} is selected from: H, C_1-C_5 alkyl, or benzyl.

6. A compound of Claim 5, or a pharmaceutically acceptable salt or prodrug form thereof, wherein:

R^{31} is selected from the group consisting of:

(a) a 6 membered saturated, partially saturated or aromatic carbocyclic ring substituted with 0-3 R^{10} or R^{10a};

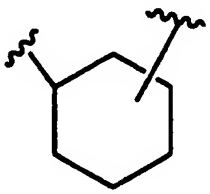
(b) a 8-11 membered saturated, partially saturated, or aromatic fused bicyclic carbocyclic ring substituted with 0-4 R^{10} or R^{10a}; or

(c) a 14 membered saturated, partially saturated, or aromatic fused tricyclic carbocyclic ring substituted with 0-4 R^{10} or R^{10a}.

7. A compound of Claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, wherein:

R^{31} is selected from the group consisting of:

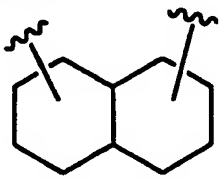
(a) a 6 membered saturated, partially saturated, or aromatic carbocyclic ring of formula:



wherein any of the bonds forming the carbocyclic ring may be a single or double bond,

and wherein said carbocyclic ring is substituted independently with 0-4 R^{10};

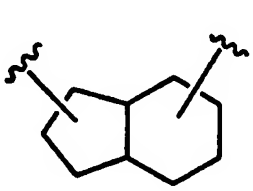
(b) a 10 membered saturated, partially saturated, or aromatic bicyclic carbocyclic ring of formula:



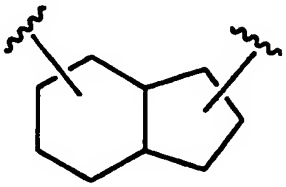
, wherein any of the bonds forming the carbocyclic ring may be a single or double bond,

and wherein said carbocyclic ring is substituted independently with 0-4 R^{10} or R^{10a};

(c) a 9 membered saturated, partially saturated, or aromatic bicyclic carbocyclic ring of formula:



or

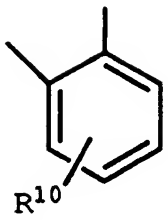


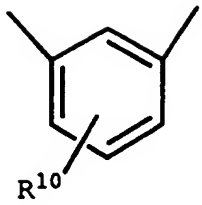
, wherein any of the bonds forming the carbocyclic ring may be a single or double bond,

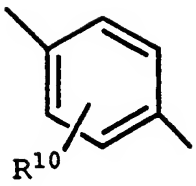
and wherein said carbocyclic ring is substituted independently with 0-4 R^{10} or R^{10a}.

8. A compound of Claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, wherein:

R^{31} is selected from (the dashed bond may be a single or double bond):

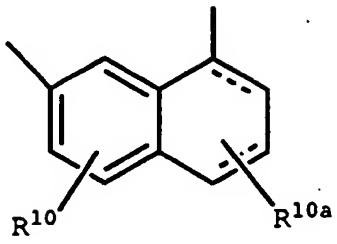


; 

; 

;

or



;

wherein R^{31} may be substituted independently with 0-3 R^{10} or R^{10a};

n" is 0 or 1;

n' is 0-2.

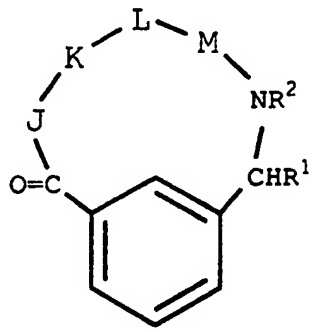
9. A compound of Claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, wherein:

R^1 and R^{22} are independently selected from:

phenyl, benzyl, phenethyl, phenoxy, benzyloxy, halogen, hydroxy, nitro, cyano, C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_7-C_{10} arylalkyl, C_1-C_5 alkoxy, $-CO_2R^{13}$, $-C(=O)NHOR^{13a}$, $-C(=O)NHN(R^{13})_2$, $=NOR^{13}$, $-B(R^{34})(R^{35})$, C_3-C_6 cycloalkoxy, $-OC(=O)R^{13}$, $-C(=O)R^{13}$, $-OC(=O)OR^{13a}$, $-OR^{13}$, $-(C_1$-C_4 alkyl$)-OR^{13}$, $-N(R^{13})_2$, $-OC(=O)N(R^{13})_2$, $-NR^{13}C(=O)R^{13}$, $-NR^{13}C(=O)OR^{13a}$, $-NR^{13}C(=O)N(R^{13})_2$, $-NR^{13}SO_2N(R^{13})_2$, $-NR^{13}SO_2R^{13a}$, $-SO_3H$, $-SO_2R^{13a}$, $-S(=O)R^{13a}$, $-SR^{13}$, $-SO_2N(R^{13})_2$, C_2-C_6 alkoxyalkyl, methylenedioxy, ethylenedioxy,

C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylcarbonyloxy, C_1-C_4 alkylcarbonyl, C_1-C_4 alkylcarbonylamino, $-OCH_2CO_2H$, 2-(1-morpholino)ethoxy, C_1-C_4 alkyl (alkyl being substituted with $-N(R^{13})_2$, $-CF_3$, NO_2, or $-S(=O)R^{13a}$).

10. A compound of Claim 1, or a pharmaceutically acceptable salt or prodrug form thereof, of the formula (II):



(II)

wherein:

the phenyl ring in formula (II) may be further substituted with 0-3 R^{10};

R^{10} is selected independently from: H, C_1-C_8 alkyl, phenyl, halogen, or C_1-C_4 alkoxy;

R^1 is H, C_1-C_4 alkyl, phenyl, benzyl, or phenyl-(C_1-C_4)alkyl;

R^2 is H or methyl;

R^{13} is selected independently from: H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, -(C_1-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

R^{13a} is C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, -(C_1-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

when two R^{13} groups are bonded to a single N, said R^{13} groups may alternatively be taken together to form $-(CH_2)_{2-5}-$ or $-(CH_2)O(CH_2)-$;

R^{14} is OH, H, C_1-C_4 alkyl, or benzyl;

J is β-Ala or an L-isomer or D-isomer amino acid of structure $-N(R^3)C(R^4)(R^5)C(=O)-$, wherein:

R^3 is H or CH_3;

R^4 is H or C_1-C_3 alkyl;

R^5 is H, C_1-C_8 alkyl, C_3-C_6 cycloalkyl, C_3-C_6 cycloalkylmethyl, C_1-C_6 cycloalkylethyl, phenyl, phenylmethyl, CH_2OH, CH_2SH, CH_2OCH_3, CH_2SCH_3, $CH_2CH_2SCH_3$, $(CH_2)_sNH_2$, $-(CH_2)_sNHC(=NH)(NH_2)$, $-(CH_2)_sNHR^{16}$, where s = 3-5; or

R^{16} is selected from:
an amine protecting group;
1-2 amino acids; or
1-2 amino acids substituted with an amine protecting group;

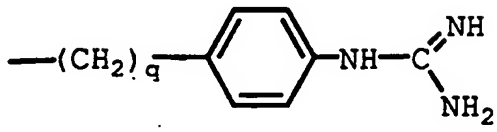
R^3 and R^5 can alternatively be taken together to form $-CH_2CH_2CH_2-$; or

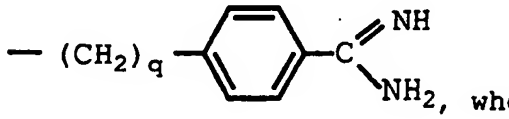
R^4 and R^5 can alternatively be taken together to form $-(CH_2)_u-$, where u = 2-5;

K is an L-isomer amino acid of structure $-N(R^6)CH(R^7)C(=O)-$, wherein:

R^6 is H or C_1-C_8 alkyl;

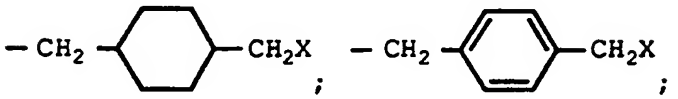
R^7 is:





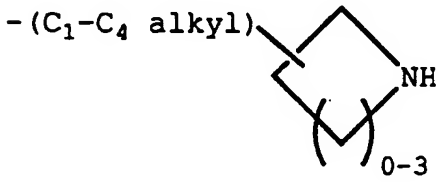
where q = 0 or 1;

$-(CH_2)_rX$, where r = 3-6;



$-(CH_2)_mS(CH_2)_2X$, where m = 1 or 2;

$-(C_3$-C_7 alkyl$)$-NH-$(C_1$-C_6 alkyl$)$



$-(CH_2)_m$-O-$(C_1$-C_4 alkyl$)$-NH-$(C_1$-C_6 alkyl), where m = 1 or 2;

$-(CH_2)_m$-S-$(C_1$-C_4 alkyl$)$-NH-$(C_1$-C_6 alkyl), where m = 1 or 2; and

X is $-NH_2$ or $-NHC(=NH)(NH_2)$; or

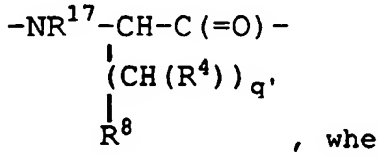
R^6 and R7 are alternatively be taken together to form

$-CH_2CH(CH_2)_nXCH_2-$, where n = 0,1 and X is $-NH_2$ or $-NHC(=NH)(NH_2)$;

L is $-Y(CH_2)_vC(=O)-$, wherein:

Y is NH, O, or S; and v = 1,2;

M is a D-isomer or L-isomer amino acid of structure



, wherein:

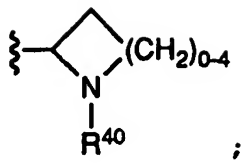
q' is 0-2;

R^{17} is H, C_1-C_3 alkyl;

R^8 is $-CO_2R^{13b}$;

R^{13b} is selected from:

(a) C_2-C_8 alkenyl;
(b) C_2-C_8 alkynyl;
(c) C_1-C_8 alkyl substituted with
  (i) aryl, optionally substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1$-C_5 alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);
  (ii) C_3-C_8 cycloalkyl;

(iii) 

;

(e) aryl, substituted with 1-2 substituents independently selected from halogen, phenyl, C_1-C_5 alkyl, C_1-C_5 alkoxy, NO_2, $-S(O)_{0-2}(C_1-C_5$ alkyl), OH, $N(R^{13})_2$, CO_2R^{13}, $CON(R^{13})_2$ or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(f) C_2-C_8 alkyl, alkenyl or alkynyl; substituted with 1-2 substituents independently selected from C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_1-C_5 alkoxy, phenoxy, benzyloxy, halogen, NO_2, CN, CO_2R^{13}, $CON(R^{13})_2$, $N(R^{36})COR^{36}$, morpholino, 2-(1-morpholino)ethoxy, $N(R^{13})_2$, $N^+(R^{13})_3$, OCOCH3, CF_3, $S(O)_{0-2}R^{13a}$;

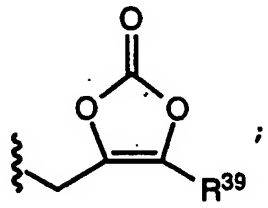
(g) $CH(R^{36})OR^{38}$;

(h) $CH(R^{36})OC(=O)R^{37}$;

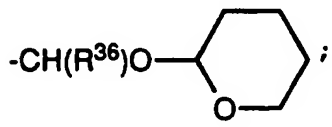
(i) $CH(R^{36})OC(=O)OR^{38}$;

(j) $CH(R^{36})OC(=O)N(R^{37})_2$;

(k) $CH(R^{36})CO_2R^{37}$;

(l) 

;

(m) 

;

R^{36} is selected independently from: H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, phenyl, or benzyl;

R^{37} is selected from:

(a) H;

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, -S(C_1-C_5 alkyl), -SO(C_1-C_5 alkyl), -SO_2(C_1-C_5 alkyl), -OH, -N(R^{13})$_2$, -CO_2R^{13}, -C(=O)N(R^{13})$_2$, or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, -S(C_1-C_5 alkyl), -SO(C_1-C_5 alkyl), -SO_2(C_1-C_5 alkyl), -OH, -N(R^{13})$_2$, -CO_2R^{13}, -C(=O)N(R^{13})$_2$, or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

R^{38} is selected from:

(a) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, -S(C_1-C_5 alkyl), -SO(C_1-C_5 alkyl), -SO_2(C_1-C_5 alkyl), -OH, -N(R^{13})$_2$, -CO_2R^{13}, -C(=O)N(R^{13})$_2$, or -C_vF_w where v = 1 to 3 and w = 1 to (2v+1);

(b) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), -OH, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{39} is selected from:

(a) H

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_6 alkyl;

(ii) C_1-C_6 alkoxy;

(iii) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), -OH, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), -OH, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{40} is selected from: H, C_1-C_5 alkyl, or benzyl.

11. A compound of Claim 10, or a pharmaceutically acceptable salt or prodrug form thereof, wherein:

the phenyl ring in formula (II) may be further substituted with 0-2 R^{10} or R^{10a};

R^{10} or R^{10a} are selected independently from: H, C_1-C_8 alkyl, phenyl, halogen, or C_1-C_4 alkoxy;

R^1 is H;

R^2 is H;

R^{13} is selected independently from: H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, -(C_1-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

R^{13a} is C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_4-C_{12} alkylcycloalkyl, aryl, -(C_1-C_{10} alkyl)aryl, or C_3-C_{10} alkoxyalkyl;

when two R^{13} groups are bonded to a single N, said R^{13} groups may alternatively be taken together to form $-(CH_2)_{2-5}-$ or $-(CH_2)O(CH_2)-$;

R^{14} is OH, H, C_1-C_4 alkyl, or benzyl;

J is β-Ala or an L-isomer or D-isomer amino acid of formula $-N(R^3)CH(R^5)C(=O)-$, wherein:

R^3 is H and R^5 is H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, $CH_2CH_2SCH_3$, $CH_2CH(CH_3)_2$, $(CH_2)_4NH_2$, (C_3-C_5 alkyl)NHR^{16};
or

R^3 is CH_3 and R^5 is H; or

R^3 and R^5 can alternatively be taken together to form $-CH_2CH_2CH_2-$;

R^{16} is selected from:

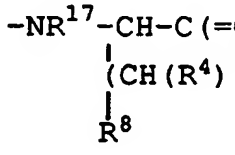
an amine protecting group;
1-2 amino acids;
1-2 amino acids substituted with an amine protecting group;

K is an L-isomer amino acid of formula $-N(CH_3)CH(R^7)C(=O)-$, wherein:

R^7 is $-(CH_2)_3NHC(=NH)(NH_2)$;

L is $-NHCH_2C(=O)-$; and

M is a D-isomer or L-isomer amino acid of structure



, wherein:

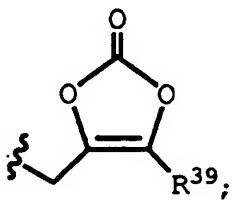
q' is 1;

R^4 is H or CH_3;

R^{17} is H;

R^8 $-CO_2R^{13b}$;

R^{13b} is selected independently from:
$-CH(R^{36})OC(=O)R^{37}$;
$-CH(R^{36})OC(=O)OR^{38}$;



R^{36} is C_1-C_4 linear alkyl or H;

R^{37} is selected from:

(a) H;

(b) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(c) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{38} is selected from:

(a) C_1-C_8 alkyl or C_3-C_8 cycloalkyl, said alkyl or cycloalkyl being substituted with 1-2 groups independently selected from:

(i) C_1-C_4 alkyl;

(ii) C_3-C_8 cycloalkyl;

(iii) C_1-C_5 alkoxy;

(iv) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1-C_5$ alkyl), $-SO(C_1-C_5$ alkyl), $-SO_2(C_1-C_5$ alkyl),

$-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

(b) aryl substituted with 0-2 groups independently selected from: halogen, phenyl, C_1-C_6 alkyl, C_1-C_6 alkoxy, NO_2, $-S(C_1$-C_5 alkyl), $-SO(C_1$-C_5 alkyl), $-SO_2(C_1$-C_5 alkyl), $-OH$, $-N(R^{13})_2$, $-CO_2R^{13}$, $-C(=O)N(R^{13})_2$, or $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1);

R^{39} is C_1-C_4 alkyl, benzyl, or phenyl.

12. A compound of Claim 10, or a pharmaceutically acceptable salt form thereof, wherein:

R^1 and R^2 are independently selected from H, methyl;

J is selected from D-Val, D-2-aminobutyric acid, D-Leu, D-Ala, Gly, D-Pro, D-Ser, D-Lys, β-Ala, Pro, Phe, NMeGly, D-Nle, D-Phg, D-Ile, D-Phe, D-Tyr, Ala, N^{ε}-p-azidobenzoyl-D-Lys, N^{ε}-p-benzoylbenzoyl-D-Lys, N^{ε}-tryptophanyl-D-Lys, N^{ε}-o-benzylbenzoyl-D-Lys, N^{ε}-p-acetylbenzoyl-D-Lys, N^{ε}-dansyl-D-Lys, N^{ε}-glycyl-D-Lys, N^{ε}-glycyl-p-benzoylbenzoyl-D-Lys, N^{ε}-p-phenylbenzoyl-D-Lys, N^{ε}-m-benzoylbenzoyl-D-Lys, N^{ε}-o-benzoylbenzoyl-D-Lys, D-norvaline;

K is selected from NMeArg, Arg;

L is selected from Gly, β-Ala, Ala;

M is selected from the group consisting of:
Asp-(methylcarbonyloxymethyl ester);
Asp-(ethylcarbonyloxymethyl ester);
Asp-(*t*-butylcarbonyloxymethyl ester);
Asp-(cyclohexylcarbonyloxymethyl ester);

Asp-(1-(methylcarbonyloxy)ethyl ester);
Asp-(1-(ethylcarbonyloxy)ethyl ester);
Asp-(1-(t-butylcarbonyloxy)ethyl ester);
Asp-(1-(cyclohexylcarbonyloxy)ethyl ester);
Asp-(*i*-propyloxycarbonyloxymethyl ester);
Asp-(cyclohexylcarbonyloxymethyl ester);
Asp-(*t*-butyloxycarbonyloxymethyl ester);
Asp-(1-(i-propyloxycarbonyloxy)ethyl ester);
Asp-(1-(cyclohexyloxycarbonyloxy)ethyl ester);
Asp-(1-(*t*-butyloxycarbonyloxy)ethyl ester);
Asp-(dimethylaminoethyl ester);
Asp-(diethylaminoethyl ester);
Asp-((1,3-dioxa-5-methyl-cyclopenten-2-one-4-yl)methyl ester);
Asp-((5-(*t*-butyl)-1,3-dioxa-cyclopenten-2-one-4-yl)methyl ester);
Asp-((1,3-dioxa-5-phenyl-cyclopenten-2-one-4-yl)methyl ester); and
Asp-(1-(2-(2-methoxypropyl)carbonyloxy)ethyl ester).

13. A compound of Claim 10, or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently selected from H, methyl;

J is selected from: D-Val, D-2-aminobutyric acid, D-norvaline, D-Leu, D-Ala, Gly, D-Pro, D-Ser, D-Lys, β-Ala, Pro, Phe, NMeGly, D-Nle, D-Phg, D-Ile, D-Phe, D-Tyr, Ala;

K is selected from NMeArg;

L is Gly;

M is selected from the group consisting of:
Asp-(methylcarbonyloxymethyl ester);
Asp-(ethylcarbonyloxymethyl ester);
Asp-(*t*-butylcarbonyloxymethyl ester);
Asp-(cyclohexylcarbonyloxymethyl ester);
Asp-(1-(methylcarbonyloxy)ethyl ester);
Asp-(1-(ethylcarbonyloxy)ethyl ester);
Asp-(1-(t-butylcarbonyloxy)ethyl ester);
Asp-(1-(cyclohexylcarbonyloxy)ethyl ester);
Asp-(*i*-propyloxycarbonyloxymethyl ester);
Asp-(cyclohexylcarbonyloxymethyl ester);
Asp-(*t*-butyloxycarbonyloxymethyl ester);
Asp-(1-(i-propyloxycarbonyloxy)ethyl ester);
Asp-(1-(cyclohexyloxycarbonyloxy)ethyl ester);
Asp-(1-(*t*-butyloxycarbonyloxy)ethyl ester);
Asp-(dimethylaminoethyl ester);
Asp-(diethylaminoethyl ester);
Asp-((1,3-dioxa-5-methyl-cyclopenten-2-one-4-yl)methyl ester);
Asp-((5-(*t*-butyl)-1,3-dioxa-cyclopenten-2-one-4-yl)methyl ester);
Asp-((1,3-dioxa-5-phenyl-cyclopenten-2-one-4-yl)methyl ester); and
Asp-(1-(2-(2-methoxypropyl)carbonyloxy)ethyl ester).

14. A compound of Claim 10, or a pharmaceutically acceptable salt thereof, selected from the group consisting of:

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(methylcarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(ethylcarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(*t*-butylcarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(cyclohexylcarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(methylcarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(ethylcarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(t-butylcarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(cyclohexylcarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(*i*-propyloxycarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(cyclohexylcarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(*t*-butyloxycarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(i-propyloxycarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(cyclohexyloxycarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(*t*-butyloxycarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(dimethylaminoethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(diethylaminoethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-((1,3-dioxa-5-methyl-cyclopenten-2-one-4-yl)methyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-((5-(*t*-butyl)-1,3-dioxa-cyclopenten-2-one-4-yl)methyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-((1,3-dioxa-5-phenyl-cyclopenten-2-one-4-yl)methyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-Val; K is NMeArg; L is Gly; and M is Asp-(1-(2-(2-methoxypropyl)carbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(methylcarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(ethylcarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(*t*-butylcarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(cyclohexylcarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(methylcarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(ethylcarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(t-butylcarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(cyclohexylcarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(*i*-propyloxycarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(cyclohexylcarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(*t*-butyloxycarbonyloxymethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(i-propyloxycarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(cyclohexyloxycarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(*t*-butyloxycarbonyloxy)ethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(dimethylaminoethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(diethylaminoethyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-((1,3-dioxa-5-methyl-cyclopenten-2-one-4-yl)methyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-((5-(*t*-butyl)-1,3-dioxa-cyclopenten-2-one-4-yl)methyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-((1,3-dioxa-5-phenyl-cyclopenten-2-one-4-yl)methyl ester);

the compound of formula (II) wherein R^1 and R^2 are H; J is D-2-aminobutyric acid; K is NMeArg; L is Gly; and M is Asp-(1-(2-(2-methoxypropyl)carbonyloxy)ethyl ester).

15. A method for the treatment of thromboembolic disorders which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 1-14.

16. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1-14 and a pharmaceutically acceptable carrier.

17. A method for lysing a blood clot which comprises administering to a host in need of such treatment a therapeutically effective amount of a thrombolytic compound of Claim 1-14.

18. A method for the treatment of thromboembolic

disorders which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 1-14 and a therapeutically effective amount of an orally active anti-coagulant agent.

19. A method of Claim 18 wherein the orally active anti-coagulant agent is selected from the group consisting of warfarin and heparin.

20. A method for the treatment of thromboembolic disorders which comprises administering to a host in need of such treatment a therapeutically effective amount of an antiplatelet compound of Claim 1-14 and a therapeutically effective amount of second anti-platelet agent.

21. A method of Claim 40 wherein the second anti-platelet agent is selected from the group consisting of aspirin, ibuprofen, naproxen, sulindae, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam and ticlopidine.

22. A method for the treatment of thromboembolic disorders which comprises administering to a host in need of such treatment a therapeutically effective amount of a compound of Claim 1-14 and a therapeutically effective amount of a thrombin inhibitor.

23. A method of Claim 22 wherein the thrombin inhibitor is selected from the group consisting of hirudin, hirudin analogs, or argatroban.

24. A method for the treatment of thromboembolic disorders which comprises administering to a host in need of such treatment a therapeutically effective

amount of a compound of Claim 1-14 and a therapeutically effective amount of a second thrombolytic agent.

25. A method of Claim 24 wherein the second thrombolytic agent is selected from the group consisting of tissue plasminogen activator, anistreplase, urokinase and streptokinase.

FIG. 1a

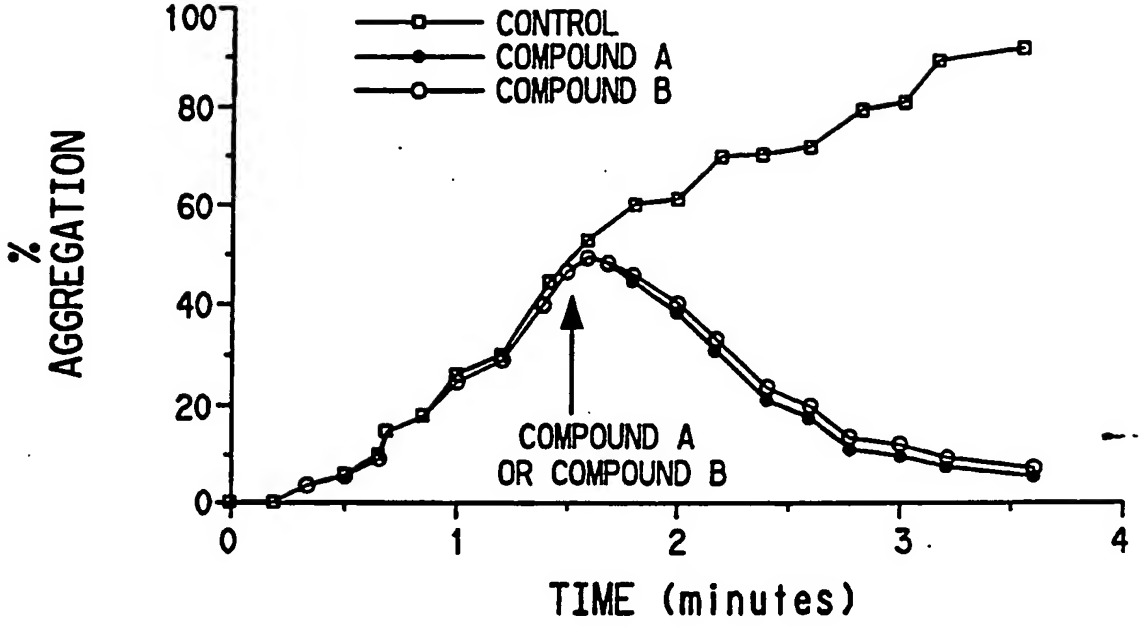

CONTROL
COMPOUND A
COMPOUND B
% AGGREGATION
100
80
60
40
20
0
COMPOUND A
OR COMPOUND B
0
1
2
3
4
TIME (minutes)

FIG. 1b

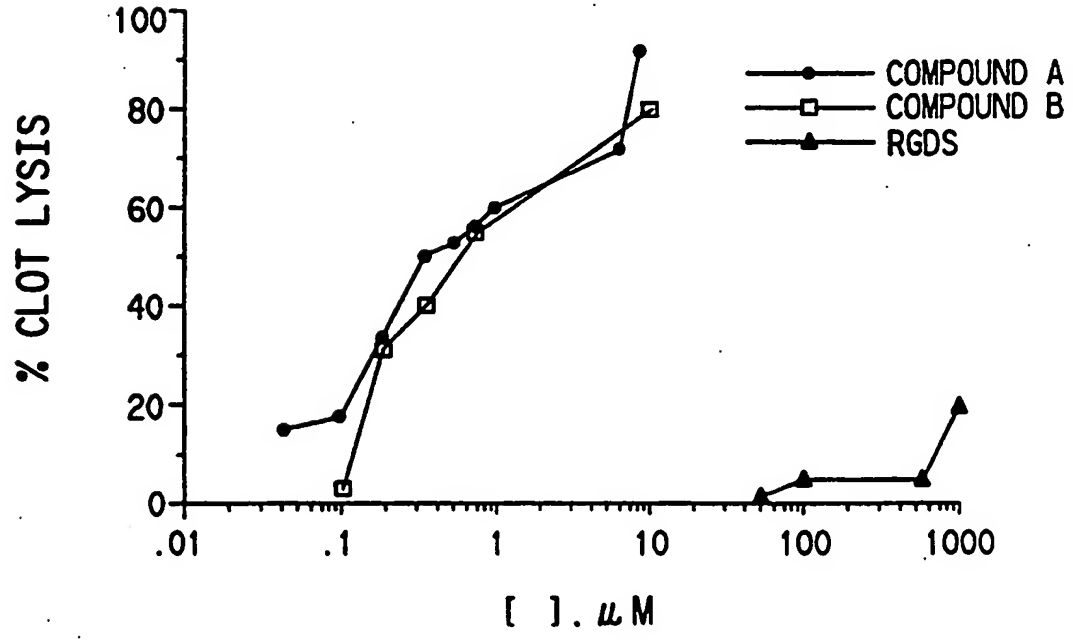

COMPOUND A
COMPOUND B
RGDS
% CLOT LYSIS
100
80
60
40
20
0
.01
.1
1
10
100
1000
[ ]. μM

FIG.2

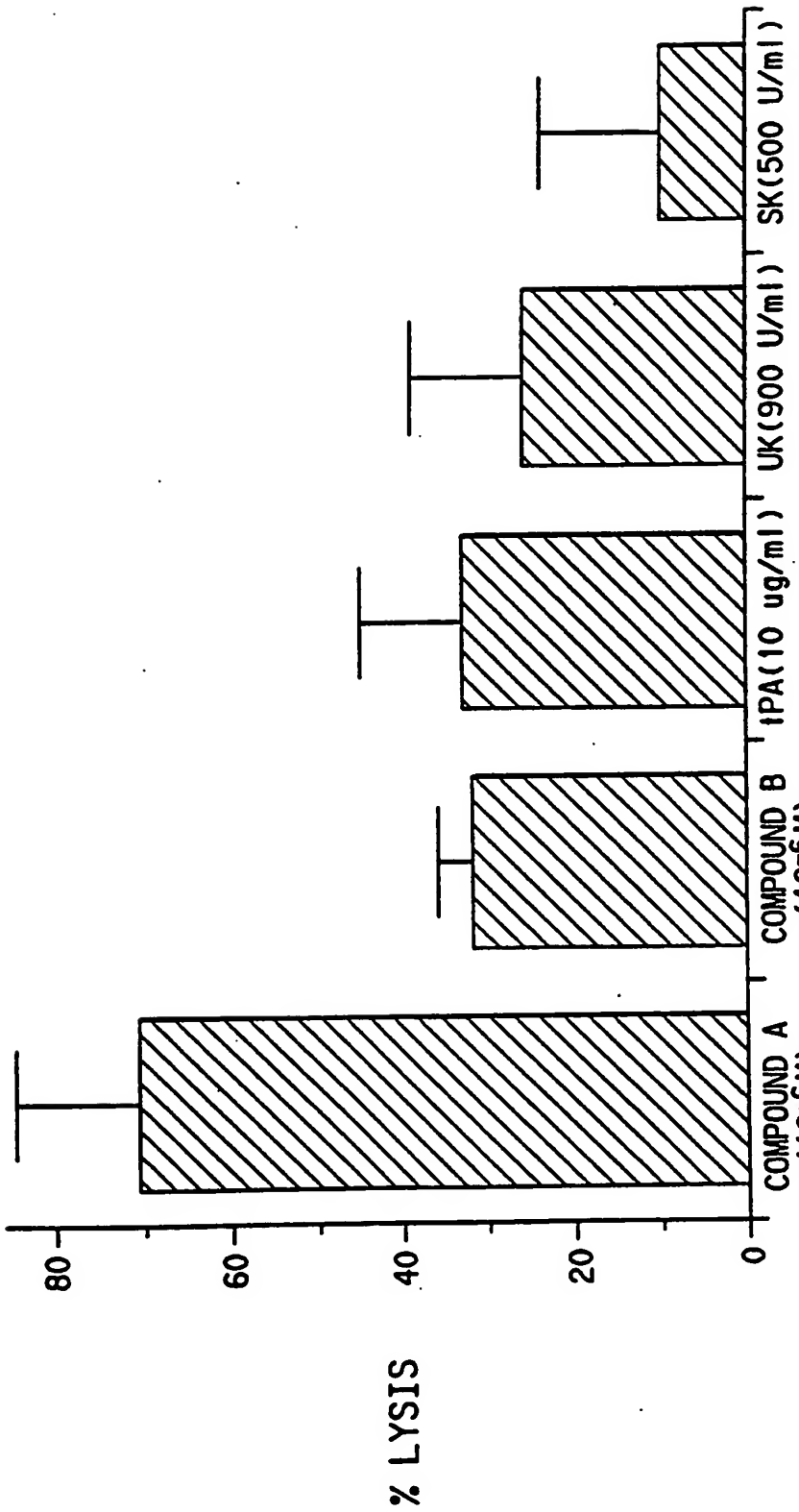

% LYSIS
0
20
40
60
80
COMPOUND A (10-6 M)
COMPOUND B (10-6 M)
tPA(10 ug/ml)
UK(900 U/ml)
SK(500 U/ml)

FIG.3

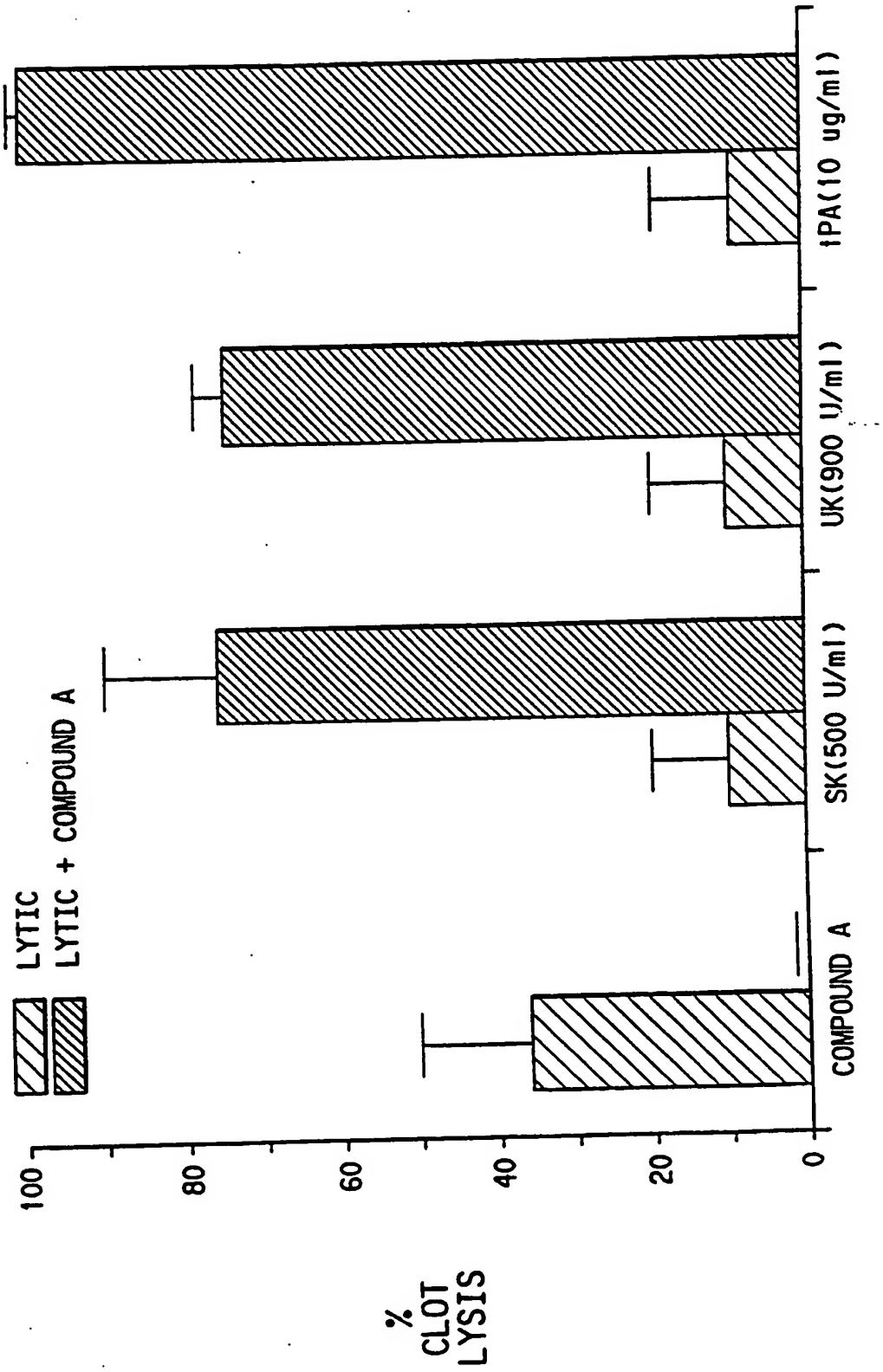

% CLOT LYSIS
100
80
60
40
20
0
LYTIC
LYTIC + COMPOUND A
COMPOUND A
SK(500 U/ml)
UK(900 U/ml)
tPA(10 ug/ml)

FIG.4

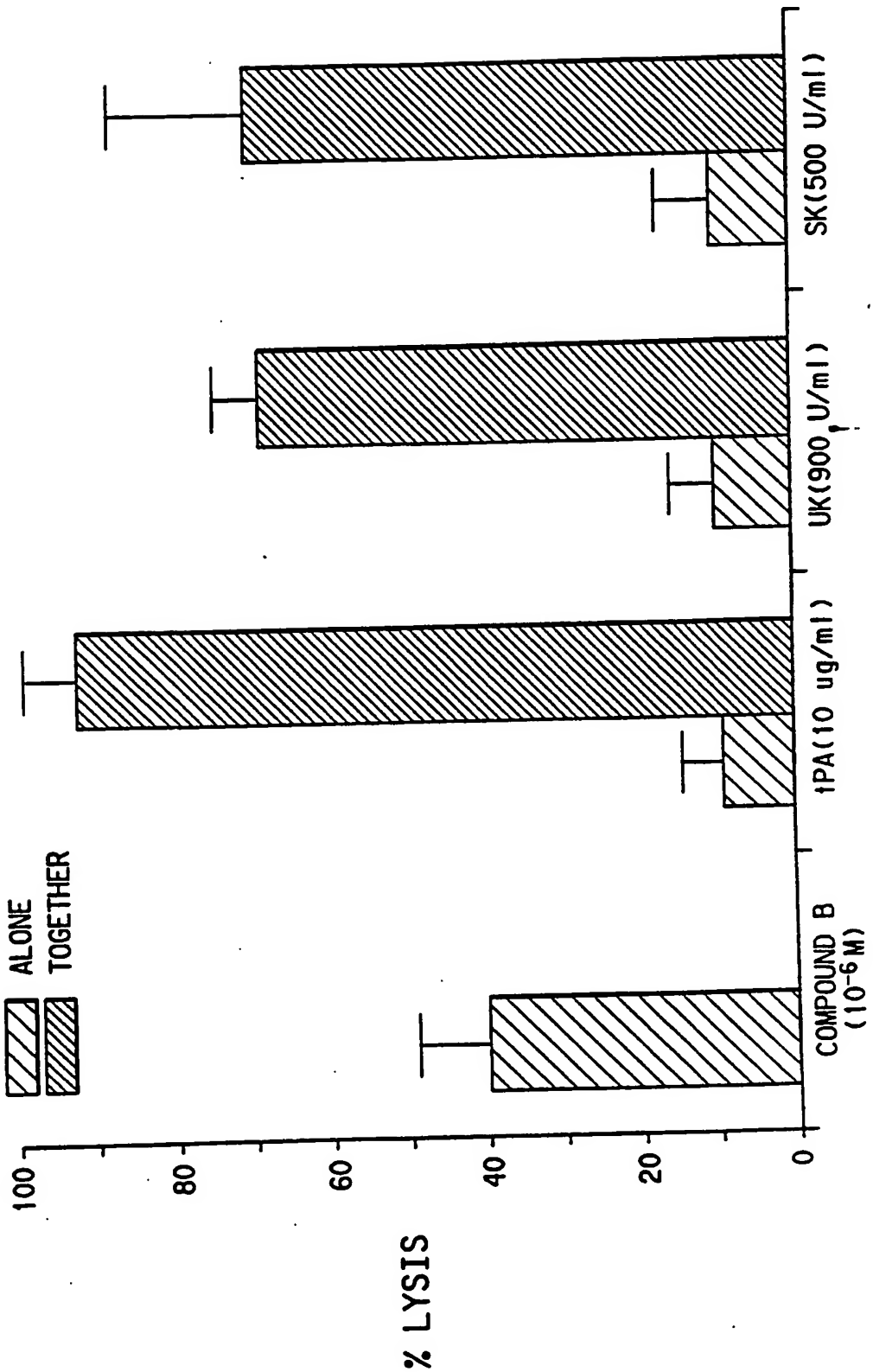

% LYSIS
100
80
60
40
20
0
ALONE
TOGETHER
COMPOUND B
(10⁻⁶ M)
tPA(10 ug/ml)
UK(900 U/ml)
SK(500 U/ml)

FIG.5

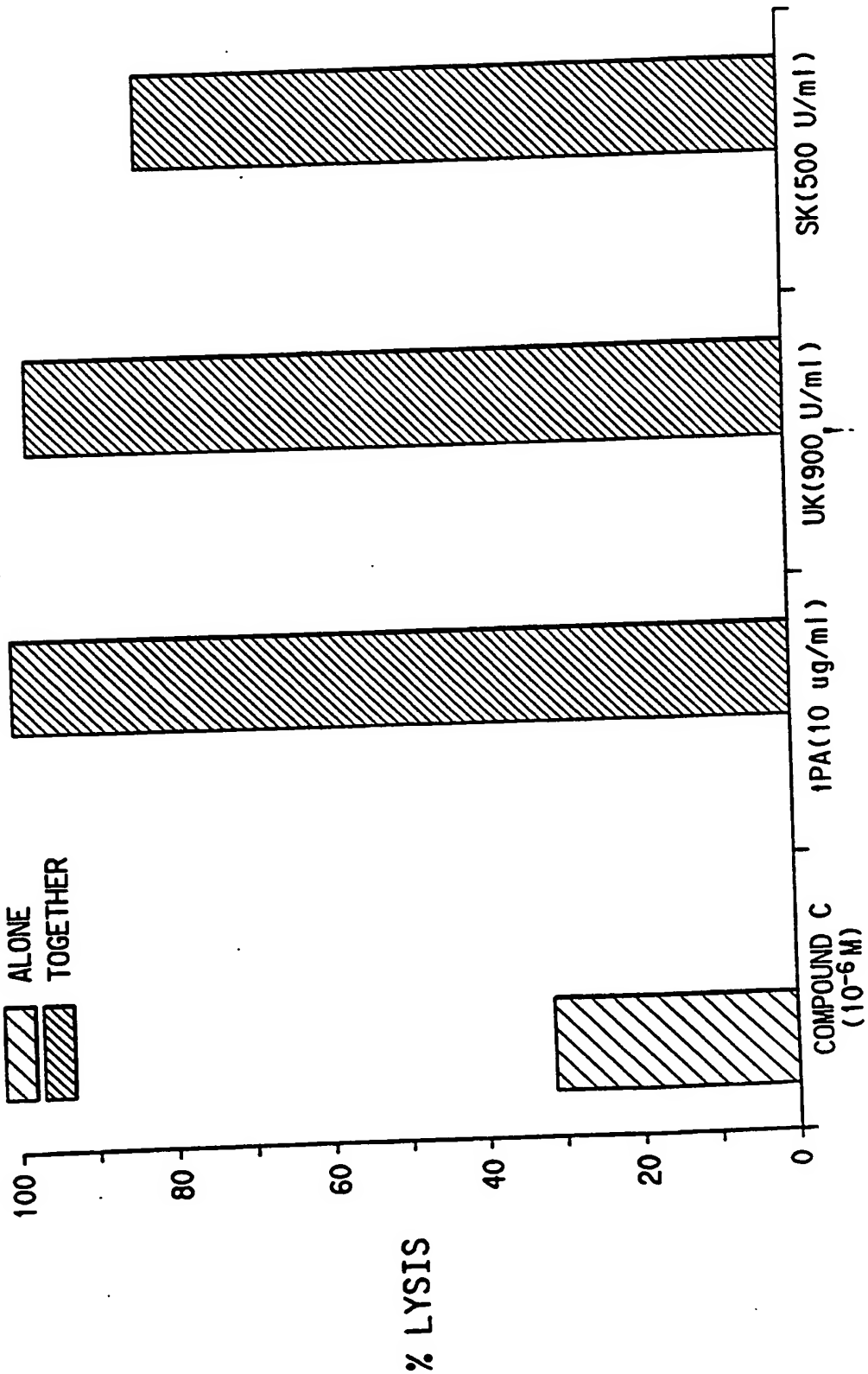

% LYSIS
100
80
60
40
20
0
ALONE
TOGETHER
COMPOUND C (10⁻⁶M)
tPA(10 ug/ml)
UK(900 U/ml)
SK(500 U/ml)

FIG.6

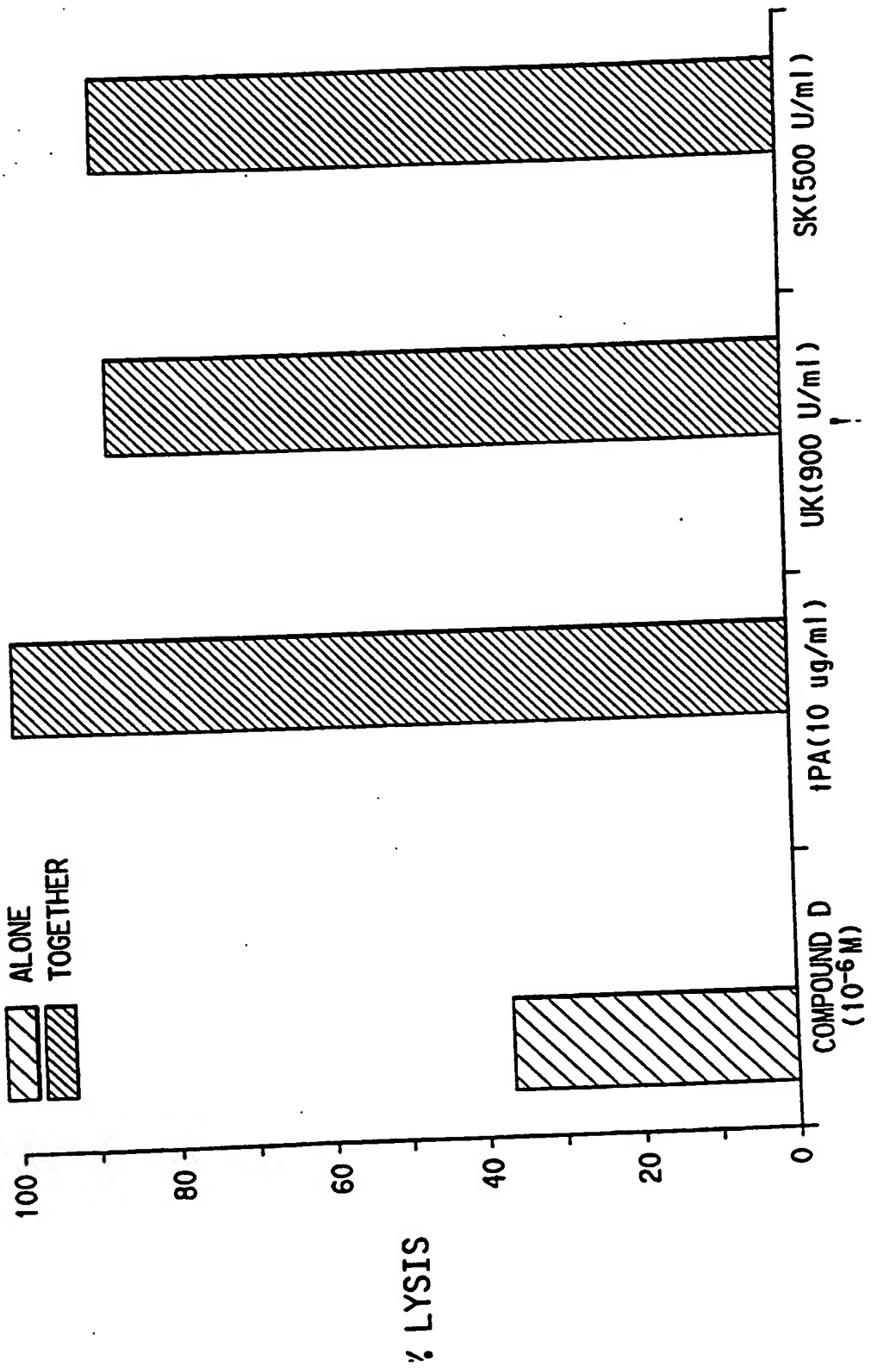

% LYSIS
100
80
60
40
20
0
ALONE
TOGETHER
COMPOUND D (10⁻⁶ M)
tPA(10 ug/ml)
UK(900 U/ml)
SK(500 U/ml)

FIG.7

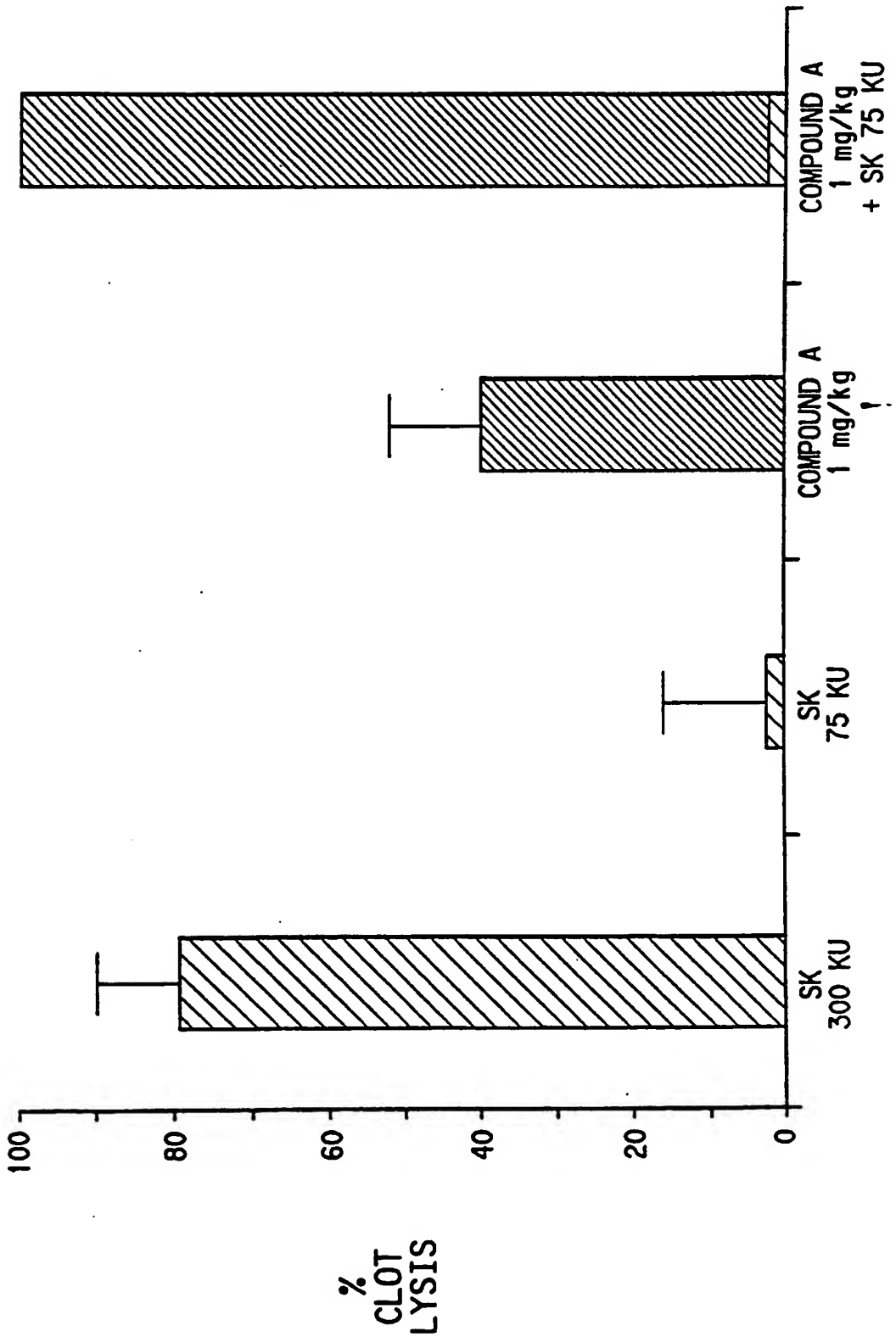

% CLOT LYSIS
100
80
60
40
20
0
SK 300 KU
SK 75 KU
COMPOUND A 1 mg/kg
COMPOUND A 1 mg/kg + SK 75 KU

FIG.8b

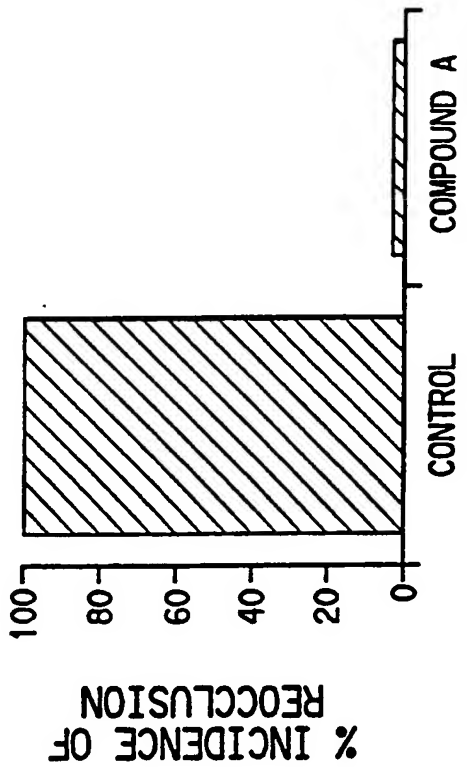

% INCIDENCE OF REOCCLUSION
100
80
60
40
20
0
CONTROL
COMPOUND A

FIG.8a

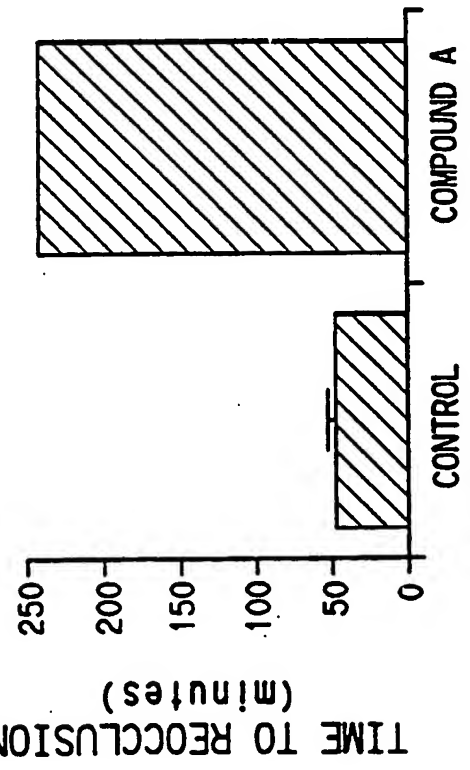

TIME TO REOCCLUSION (minutes)
250
200
150
100
50
0
CONTROL
COMPOUND A

FIG.8d

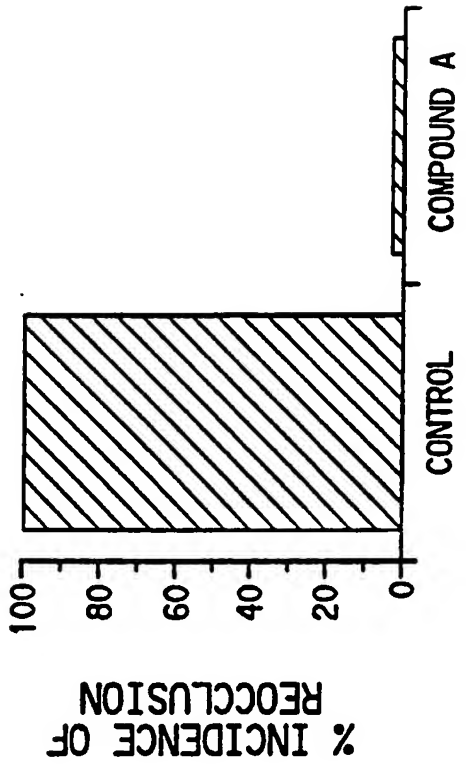
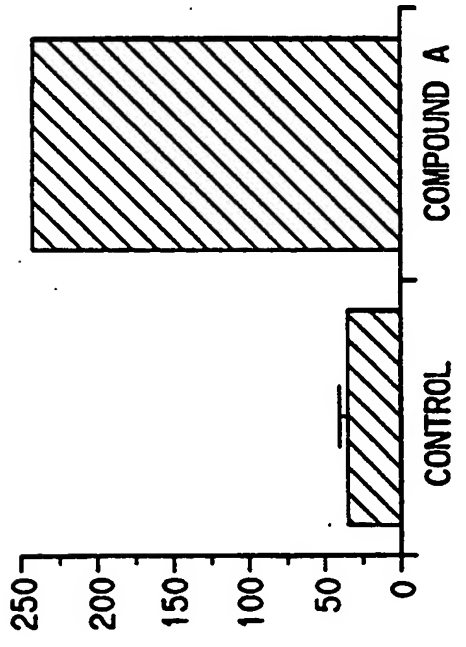

% INCIDENCE OF REOCCLUSION
100
80
60
40
20
0
CONTROL
COMPOUND A

FIG.8c


TIME TO REOCCLUSION (minutes)
250
200
150
100
50
0
CONTROL
COMPOUND A

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/US 94/03223

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07K5/12 C07K7/56 A61K37/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,93 07170 (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 15 April 1993 * claims 1-9,12-34 *	12-25
Y	EP,A,0 425 212 (SMITHKLINE BEECHAM) 2 May 1991 * claim 1; pages 3-4 *	12-25
Y	WO,A,91 01331 (GENENTECH) 7 February 1991 * claims 1-4,39-48,59; pages 1-3 *	12-25
A	WO,A,90 02750 (CNRS) 22 March 1990 * claims *	12-25

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 July 1994	09. 08. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Hermann, R

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I .national application No.
PCT/US 94/ 03223

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-11
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
see annex

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Claims 1-11 of the present patent application do not comply with the requirements of Article 6 PCT to such an extent that it is not possible to carry out a meaningful search.
No special search effort can be made for searching unduly wide or speculative claims.

As a matter of principle, a formula consisting virtually completely of variables with cascading significations is hardly a permissible generalisation which is fairly based on experimental evidence.
Claims 1-11 cannot be regarded as "clear and concise description of the matter for which protection is sought".

The search has been limited to claim 12, and subject-matter depending thereof or relating thereto (see Art. 17(2)(a)ii PCT).

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/US 94/03223

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